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## Mud therapy and rehabilitation - scientific relevance in the last six years (2015 – 2020) Systematic literature review and meta-analysis based on the PRISMA paradigm



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### Abstract

**Background.** Balneotherapy is a stimulation - adaptation treatment method applied in the forms of bathing, drinking, and inhalation cures performed with natural therapeutic factors, a method which is acting in three main ways: thermally, mechanically, and chemically. Mud or peloids are natural therapeutic factors formed by natural processes under the influence of biological and geological phenomena, which in a finely dissolved state and mixed with water (mud) are used in medical practice in the form of baths or local procedures.

**Objective.** This systematic review aims to rigorously select related articles and identify within their content, the main possible uses of therapeutic mud and physiological mechanisms, to see the main region of scientific interest for pelotherapy, and to discuss the value of mud therapy in rehabilitation medicine.

**Methods.** The working method is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched for open-access articles published in English, between January 2015 and December 2020, from the following databases: Cochrane, Elsevier, NCBI/PubMed, NCBI/PMC, PEDro, and ISI Web of Knowledge/Science (the latter was also used to identify ISI indexed articles). The contextually searched syntax used was "Pelotherapy/Peloidotherapy/Mud-therapy/ /Fango-therapy AND Rehabilitation". The selected articles were analyzed in detail regarding pathologies addressed by mud therapy and country scientific relevance for this therapeutic method. The meta-analysis proceeded was designated to estimate the prevalence of various pathologies in the use of mud therapy.

**Results.** Our search identified, first, **394** articles. Based on the successive filtering stages and, respectively, on the classification criteria of the Physiotherapy Evidence Database (PEDro), we finally identified/retained and analyzed **68** articles. Although, in principle, a rigorous method – and we have followed the PRISMA type paradigm – there still might be some missing works of our related article selection. On the other hand, to augment/ consolidate our documentation base, we have used also **40** papers freely found in the literature, and even – aiming, too, at an as exhaustive knowledge underpinning as possible – derogatively, we have also considered some articles which, probably being very new, couldn't yet have reached the PEDro threshold score we have settled.

**Conclusions.** This paper overviews the current state-of-the-art knowledge in the approach of peloidotherapy in rehabilitation, with a focal point on the therapeutic properties of peloids.

**Keywords:** mud-therapy, pelotherapy, peloidotherapy, fango therapy, rehabilitation, balneotherapy, natural therapeutic factors,

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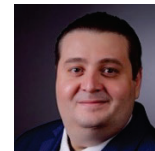
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## 1. INTRODUCTION

Collectively, the spa economy is estimated at \$94 billion, with a consistent growth perspective in the coming decades. The general context of spa environments can support a holistic approach to health promotion (1).

Basic components of health resort interventions - spa therapies (2) - are balneotherapy (3) and climatotherapy. In many countries, treatments involving natural mineral waters, gases, or peloids (4) are referred to as balneotherapy. Routes of application include bathing, inhalations, drinking (Crenotherapy), etc. (5), often encompassing rehabilitation objectives/procedures (6)(7). According to the definition given by the "International Society of Medical Hydrology", muds (peloids) and clays (8) are "substances formed in natural conditions under the influence of geological processes and which, mixed with water (9), are used in medical practice in the form of baths or local procedures (10).

Muds are earths or rocks of a pasty consistency, used as therapeutic remedies or cosmetics (11) from remote times. Some beneficial effects of mud are known empirically from antiquity, others have been described and studied quite recently, some have remained today in the stage of summary explanation. Mud treatment is also called pelotherapy (9), peloidotherapy, or sometimes – a largely – fango therapy. Pelotherapy should be used only as directed and under medical supervision (8).

From ancient times people used mud, when they had it at their disposal, for healing or beautification (12). Archaeological artifacts support such a hypothesis and there are no problems in understanding these data since the instinct to seek healing remedies also exists for the animal world, argued by new data also (13). Even if images in which the pig rolls in the mud for comfort seem legendary, or from a fairy-tale, we can only admit that such behavior is explainable in the equation of an adaptive benefit. The use of mud has its origins in antiquity. In ancient Egypt, the sick were anointed with the mud brought by the Nile during the floods.

The most common therapeutic muds are deposits in saline basins - black sulfurous muds, which form on the bottom of marine estuaries, bays, and continental salt lakes. The activity of quality evaluation for the resources of natural therapeutic substances begins by taking samples at source and ends with their complex interdisciplinary characterization, being developed indications and contraindications for prophylaxis, therapy and/or rehabilitation by conducting a complete pharmacodynamic study.

In one of his works, Pliny (23-79 AD) recommends the use of mud, a recommendation made by Dioskorides (50 AD) in his works and later also by Galen (131-202 AD). In antiquity, Cleopatra's behavior is historically emphasized, considered a beauty of her time, in terms of bodily maintenance, an aspect directly correlated with

skin health. The beneficial effects of the mud and salt from the Dead Sea (11) led her to ask Marc Antonius to conquer this region to benefit from this remedy. Therefore, the use of Dead Sea (14) mud for therapeutic purposes dates back thousands of years, from the time of the Roman Empire.

We have more accurate data on the use of mud from the 14th century, in a paper that talks about the use of therapeutic mud from Albano and Battaglia, and Fallopius describes in 1564 the technique of using mud. Later, mud therapy (pelotherapy/peloidotherapy) is used in France (seventeenth century) and Germany (eighteenth century). In Russia, the cradle of pelotherapy is the Crimean peninsula.

Last but not least, Romania is a country famous for its balneary resorts. For renowned mud deposits, Techirghiol, Sovata, Ocna Sibiului, Mangalia, Amara are the main resorts promoted for mud therapy.

The complex interdisciplinary characterization of the natural therapeutic factors necessarily includes interpretation of physicochemical analyzes and microbiological (15)(16) examinations.

### **Classification of muds (17)**

**Clay** (18) has been used by humans since before recorded history to accomplish basic but fundamental healthcare purposes. The clay plates of Nippur, Mesopotamia, which date back to about 2500 BC, contain a reference to the use of clays for therapeutic purposes, including the treatment of wounds and the inhibition of hemorrhages. Also, the famous Papyrus Ebers dated about 1600 BC describes the treatment of some diseases using clay-based medicines. Since then, from Ancient Greece, Roman times, medieval times, renaissance times to contemporary times, there exist reports on the therapeutic, nutritional and cosmetic uses of clay and clay-based products (8). There are several types of clay and within them, the so-called healing clay (19) and edible clay had been used and are still being used, by man for therapeutic, nutritional, and cosmetic purposes. Edible clay is a particular type of healing clay which use is limited to internal application through ingestion, for instance, of cookies made of clay/ /potable water dispersion/suspension. Conceptually healing clay besides the oral use for internal health benefits of the digestive tract (20) can also be used in external or topical applications as clay and mineral water paste called mud or peloid for the treatment of muscle-skeletal and dermatological disorders (8)(21).

**Peloid** is a matured mud or muddy dispersion with healing and/or cosmetic properties, composed of a complex mixture of fine-grained natural materials of geologic and/or biologic origins, mineral water or seawater, and common organic compounds from biological metabolic activity.

**NATURAL peloids** are formed by depositing more or less decayed, rotten, overripe, organic, and inorganic substances in bayous, sea lagoons, saltwater and freshwater lakes, rivers, marshes, mineral water spring mires, and volcanic areas (22).

**ARTIFICIAL peloids** are natural clays that are refined and significantly changed before their use (23).

According to their origin:

**ORGANIC PELOIDS** comprise those peloids consisting of over 10% of organic substances:

- ✓ peat (peat soil, elevated and leveled peat) (24)(25)
- ✓ organic mud (bitumen mud, sapropel and Gytja)(8)

**INORGANIC PELOIDS** (8) comprise:

- ✓ mineral peloids (clay, loam, tufa)
- ✓ volcanic peloids (8)

Depending on the formation conditions and the chemical composition, the therapeutic muds are classified into:

a) **Sapropelic muds** - are represented by black deposits, rich in colloidal iron hydrosulfide, have a plastic and greasy appearance, are found on the bottom of salt waters originating from the action of microorganisms on the flora and fauna of the aquatic basin to which minerals or inorganic substances that come from the soil of the lake basin are associated. Their content in organic substances is greater than 10% to the weight of the dry matter - continental lake, lagoon;

The flora consists of microphyte and macrophyte algae in which *Cladophora vagabunda*, *Cladophora cristalina*, predominates, algae that grow only in saltwater.

The aquatic fauna is represented by the species *Artemia salina* 10 - 12 mm, red arthropods. The carcasses of *Artemia salina*, by bacterial decomposition, together with the alga *Cladophora cristalina*, form the sapropelic mud. Sapropelic muds are black deposits underwater sediments rich in colloidal iron hydrosulfide, plastic and greasy.

b) **Mineral and vegeto-mineral muds** appear by sedimentation of the salts of some springs with sulfidic, ferruginous, carbogazeous character. Mineral muds - arise by the sedimentation of salts of carbonaceous, calcium, ferruginous or sulfurous springs;

c) **Peat** (*humus vegetabilis lutosus*) - organic, brown mud. Peat muds result from the microbiological decomposition of the remains of vegetables accumulated on the bottom of some swamps. Their content in organic substances is also greater than 10% of the weight of the dry matter (24). Peat is formed in the following ways:

- natural formation through physicochemical and microbiological processes at the contact of the mineral water with the clay bed, around the natural emergents, resulting in the content of organic substances in dry mud below 10%;
- directed formation through microbiological and physicochemical processes at the contact of the mineral water with the clay bed - artificial basins -

resulting in the content of organic substances in dry mud below 10%;

- incomplete transformation of the vegetal material in conditions of advanced humidity - swamps, resulting in the content of organic substances in dry mud of over 10%;
- salty clays and marls, sedimented in arid land conditions - lagoons from the biological past;
- calcareous tuffs, formed by chemical precipitation - around natural carbon dioxide emergencies.

**Fango therapy** - is a particular type of pelotherapy that involves the use of fango name of Italian origin attributed to muddy natural peloids deposited from thermal springs as happens in the case of the Euganean volcanic region, in Italy, where important Thermal Resorts exist (8).

**Chemical composition of peloids** (26)(27)

From a physicochemical point of view, the mud is a heterogeneous system (28) consisting of a liquid phase containing water and water-soluble mineral salts, a solid phase containing mineral and organic substances, and a gaseous phase containing hydrogen sulfide (29).

The ionic balance of mud is also reflected in its pH. In general, the mud is alkaline pH = 9 – 10 (30).

The therapeutic effect of mud is given by the combination of its physical and chemical properties (31).

#### LIQUID PHASE

It is the solution of imbibition - the aqueous solution of organic and inorganic substances

Depending on its proportion muds are divided into:

- poorly hydrated with moisture content <37%
- medium hydrated by weight humidity = 37-40%
- strongly hydrated with a moisture content > 40%

The liquid phase results from the water of the lakes in the basin of which the mud is produced rainfall, and impact of mineral waters. Depending on the predominant ions (32), it may have a different character: sulfated, carbonated, or mixed, and with the following content:

- Water, anions, cations (33),
- Oligoelements (ug/kg) (28)
  1. with pharmacological effect (Fe, Co, J, Br, and B)
  2. involved in the enzymatic processes (J, Fe, Cu, Mo, Zn, Co, Mn, Ni, Ba, Sr, Cd)
  3. non-essential/toxic elements (As, Pb, Hg, V, and F)
  4. not yet elucidated biological role (Ti, Zr, Ir, Cs).
- Biologically active substances - protein hydrolysates, amino acids, enzymes (34).

**GASEOUS PHASE** - results from the physicochemical and biochemical processes involved in the mud formation (peloidogenesis):  $H_2S$ ,  $CO_2$ ,  $NH_4$ ,  $CH_4$ ,  $O_2$ , Rn (8)

Hydrogen sulfide ( $H_2S$ ) is also an endogenous gas with important physiological functions (35). Endogenous hydrogen sulfide has been reported to function as a neuromodulator in the brain and within the vasculature; the main functions of  $H_2S$  are vasodilation and promoting new vessel growth (36).

## SOLID PHASE

- Crystal framework (peloid skeleton) – *determines the mechanical structure*
- Oxides (SiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, Fe<sub>2</sub>O<sub>3</sub>, CaO, MgO, Na<sub>2</sub>O, K<sub>2</sub>O, TiO<sub>2</sub>, MnO, P<sub>2</sub>O<sub>5</sub>), Na<sub>2</sub>O/CaO < 1
- Colloid complex - *plastic hydrophilic basis which absorbs moisture and defines thermal properties*
- Inorganic component Fe(HS)<sub>3</sub>, Fe(OH)<sub>3</sub>, Al(OH)<sub>3</sub>, H<sub>2</sub>SiO<sub>3</sub>
- Organic component – humic substances: humin, humic and fulvic acids (34)

Humic substances are generally considered to have occurred during the humification process of the organic material. Their color varies from yellow to black, molecular mass from 2000 to over 300,000 Da, have a C content between 45 and 62%, O between 30 and 48%, and free acidity between 500 and 1400 mEq% (37).

The heterogeneity of the molecular weight of many individual compounds with different chemical compositions containing biogenic elements (C, N, O, P, S) in carboxyl, phenol, alcohol, peptide, amide, and other functional groups causes humic substances to be polydisperse, heterogeneous, biophilic and multifunctional (37).

The mud can be fractionated using the variation of pH and polarity of solvents and humic extracts can be characterized spectrophotometrically based on absorption in the wavelength range 340-700 nm, humic acids, and fulvic acids being differentiated based on solubility and molecular weight. Briefly, the mud is treated with a KOH solution, obtaining the alkaline extract of soluble humates and fulvates and the precipitation of insoluble humin(37).

### Physical properties of mud (38)(27)

- ✓ **Specific weight** - depends on the components **mineral substances > organic substances**, is maximum for strongly mineralized muds, minimum for peat muds
- ✓ **Hydropexy**: water absorption and retention capacity, practical value - peloids with low hydropexy (mineral mud) are used only for packaging, those with medium hydropexy (sapropelic mud) and high (peat mud) can also be used for baths.
- ✓ **Plasticity**: the property of stretching and molding on the surface of the body - is given by the solids in their content; low plasticity (mineral mud), medium (peat), and high (sapropelic) (25)
- ✓ **Thermopexy**: heat absorption and storage - peloids have a high ability to retain heat (39)(40).
- ✓ **Consistency** – it depends on the viscosity conditions the frictional force that is exerted on the skin when applied (40)
- ✓ **Specific heat** - represents no. of calories to raise the heat of one gram of mud by one degree (40)(41)(42)
- ✓ **Granulometry** - the degree of mud dispersion and the size of the solid particles (41)

## Methods of mud applications

- ✓ **Mud baths**, full, half body, or arm-leg - in tubs with heated lake water in which 10 - 12 kg of mud are added, progressively increasing its concentration up to 10 - 25%. The mixture can be heated to 42 ° C (43). In the case of patients with cardiovascular diseases, the temperature should not exceed 37°C, and for those with inflammatory rheumatic diseases below 36°C. The duration of the bath is 20 ' - 40'. The bath must be followed by a shower at 37° - 38°C and a rest of at least one hour. A cure consists of 12-15 daily baths.
- ✓ **Mud Packages applications**: peloids are applied to specific areas of the body (44)
- ✓ **Mud anointing** - is the oldest method that involves applying cold mud on the patient's skin, after it has been heated 10-15', in a thin layer, on limited areas or the whole body. The patient should then be exposed to the sun, in an upright position, until the mud dries, approximately 30 - 60', followed by a bath of 10' - 15' in sea or lake water accompanied by movement and a short shower with cold water and bed rest for at least an hour. It is a method of stressing the mechanisms of thermoregulation, neuroendocrine stimulation, and adaptation processes by alternating hot-cold contrasting factors.
- ✓ **Mud wraps** - consist of applying mud in a layer of 1 - 2 cm heated to 38° - 46°C on a limited region or the entire body surface for 20' - 40'.
- ✓ **Poultices** - applications with mud at different temperatures on limited regions of the body (24).
- ✓ **Gynecological applications** - in the form of vaginal swabs with mud at 39° - 40°C for 2 hours or vaginal irrigation with mud dissolved in lake water and heated to 37°C (43).
- ✓ **Mud massage** - stretching and mud massage

### Application method:

1. After application, the body gets freed of mud with the assistance of a warm shower (taken under the water in temperatures of 37-38 °C).
2. The patient gets dried of immediately and rests for half an hour to an hour.
3. Afterward, the patient either takes a light walk or receives a massage, or is taken into an adequate exercise program, if necessary.

### Main peloid actions:

- cardiovascular system - stimulation of cardiovascular reactions with accentuation of hemodynamics by central and peripheral mechanisms. Immediate mobilization of blood deposits and their involvement in the general circulation takes place; cutaneous vasodilation → increases cardiac output (45)
- nervous system - sedative or exciting effects on the CNS and SNV by sedating pain receptors (46).
- The mud bath determines the increase of the antimicrobial defense capacity by increasing the

- phagocytic power of the leukocytes - highlighted by the changes of the opsono-cytophagic index
- digestive: determines the balance of gastric secretion, increases biliary secretion
  - renal: decreases renal secretion and diuresis (when perspiration is stimulated)
  - tissue: tissue hydrophilicity changes → increases resorption capacity (chronic inflammation, bursitis)
  - immune system - regulation of immunoglobulin values (47), an increase of non-specific immunity (9)(48).
  - The endocrine system. The enzymatic and metabolic changes that appeared in the endocrine glands after peloidotherapy differ according to the specific secretion of the gland, according to the functional stage in which the gland is located, and are related to the type of therapeutic application. Under the action of mud, there is a harmonic stimulation in all glands in the sense of increasing the enzymatic and synthetic activity while maintaining the specificity of each. Correlated with the activity of endocrine functional harmonization is the stimulation of the activity of the hypothalamic-pituitary-adrenal axis translated by optimizing the plasma levels of  $\beta$ -endorphins. Glands with internal secretion - ovarian, pituitary function are stimulated.
  - The endocrine mechanism is also involved in inducing the anti-inflammatory (49) effects of pelotherapy by modulating the activity of the hypothalamic-pituitary-adrenal axis and by the general balancing of the endocrine balance, persistent effects, and post-cure.
  - Reactivity to chemical mediators - acetylcholine and adrenaline - as well as to ions correlated with vegetative activity - Ca, Mg, K - is increased after the external cure with mud, and the vegetative tone tends regulation/normalization, which leads to remediation of vegetative stigmas.

### **Therapeutic effects of mud (50)**

Through its composition and thermopexy properties, the mud determines:

- ✓ stimulation of peripheral mechanoreceptors - triggers reflex mechanisms with favorable effects;
- ✓ subsequently follows skin vasodilatation (neurohumoral phase, with input made directly through the thermal factor) - benefits the absorption of elements present in the mud;
- ✓ bacteriostatic and bactericidal effects (51)(34)
- ✓ exchanges of energy and substances (thermoregulation of peripheral circulation, excretion, stimulation of skin repair processes) (2);
- ✓ general thermoregulation stress resulting in related optimized adaptive physiology and or therapeutic-rehabilitative responses (2);
- ✓ vitamin D synthesis;

- ✓ regulating the balance of homeostasis through immune, endocrine, and neurovegetative mechanisms (47)(52);
- ✓ better oxygenation of tissues (an increase of  $SO_2\%$  in peripheral blood,  $O_2$  binding capacity, and oxy-hemoglobin).

The thermal effect of peloidotherapy determines:

- ✓ pain relief (53);
- ✓ decreased muscle contractions (54);
- ✓ anti-inflammatory effects - the higher the application temperature, the higher the tonic immuno-stimulatory and cardiovascular effects, the application is possible due to the special mud property of thermopexy.

All of these develop local and general remote effects, such as analgesic effect, anti-inflammatory, muscle relaxant, detoxifying, neuroendocrine, to regulate immunity (55) and because the (including) mud based thermotherapy acts, as well, by enhancing the elasticity of the conjunctive-collagen major musculo-entheso-articular constituents – respectively through reducing their stiffness, which is associated to many conditions affecting such structures and/or to (just) aging – this, together with the above mentioned muscle decontracturant and analgesic effects, results also in an important link to facilitating rehabilitation: with more supple, relaxed and pain freer segments of the body, is a biological state prone to better outcomes of kinesiotherapy/ physical exercise, with consequent augmented functional mobility recover, and thus, an overall improvement of the quality of life, too.

### **Pharmacodynamic properties**

Being a biological material used in human therapy, the analysis is performed according to the methods indicated in the "Romanian Pharmacopoeia" with some additions taken from the working methods used for soil analysis. The obtained result is presented in the form of the physicochemical analysis bulletin.

When applying peloids, a series of processes take place at the level of the skin:

- ✓ sensitive reception of mud qualities/properties and their transmission to the upper stages of integration and control;
- ✓ exchange of energy and substance with the peloid environment;
- ✓ fulfillment of adaptive functions: circulatory (peripheral circulation of thermoregulation), secretory (sweating), protective (keratinogenesis, melanogenesis, hydrolipid film formation);
- ✓ integration of skin - mud application effects in the general physiology of the body: thermoregulation, vitamin D synthesis, optimization of homeostatic balances: immune, endocrine, and neurovegetative of the body (17).



Applying mud to the entire surface of the skin triggers local tissue and general functional reactions, inhibiting or activating some enzyme systems and intermediate metabolites. The mud spa treatment produces favorable effects that persist for a long time by changing the ability to respond adaptively to various stimuli.

This procedure is a demanding one as the application time, density and temperature are higher, respectively the higher the salt concentration of the dilution saltwater. Even in healthy, robust patients, this procedure is especially demanding for the cardiovascular system. That is why it is contraindicated especially in hyper and hypertensive patients.

#### **Peloidotherapy is indicated for the following conditions:**

- degenerative rheumatism with different locations: spine (spondylosis, simple discopathy, chronic lumbago) (56), peripheral (coxarthrosis, gonarthrosis) (57)
- osteoarthritis (58)(59)(60)(61)(62)(63)(64)(65)(66)(67),
- inflammatory rheumatism (54)
- ab-articular rheumatism (68)
- fibromyalgia (69)(70)
- musculoskeletal disorders (MSDs) (71)(72)
- post-traumatic sequelae (73)
- carpal tunnel syndrome (74)
- central and peripheral nervous system damage (75)
- psoriasis (76)(34)
- chronic eczema, chronic wounds (77)
- chronic urticaria
- obesity (78)
- pituitary dwarf
- rickets or children's weakness
- gynecological chronic inflammation, secondary sterility, post-tuberculosis sequelae

The ability of therapeutic mud to effectively restore reproductive function has long been known and does not cause doubt. In mud resort centers for the treatment of infertility applications and mud baths, vaginal and rectal tampons with mud heated to the desired temperature.

The effect of mud therapy will be more visible if it is combined with physical therapy (79) and gynecological massage, with medical microclyms, reflexology, and homeopathy.

Mud treatment is indicated for patients with chronic inflammatory processes of different origins, with chronic adnexitis and peri-adnexitis, with different adhesions, with parameterized residues, with chronic endocervicitis and colitis, with some forms of infertility, with miscarriage.

Mud treatment is useful in case of insufficiency of ovarian function and mild forms of uterine underdevelopment. Patients with severe genital lesions at Trichomonas may go for a spa treatment. Amenorrhea and dysmenorrhea - menstrual disorders - are also indications for mud therapy.

#### **Contraindications**

- febrile/infectious or acute/subacute conditions - other than those for which the treatment is performed;
- cardiovascular diseases;
- respiratory diseases: exacerbation of COPD, asthma with recent seizures, bronchiectasis, recent respiratory infections;
- dermatological diseases: bedsores, suppurative wounds, eczema in the developmental stage, psoriatic erythroderma.

Mud therapy is contraindicated if the patient suffers from asthma, diabetes, ulcers, any form of cancer, or hepatitis, kidney, or cardiovascular disease.

#### **2. METHOD**

**Search Strategy.** To fundament the above-mentioned data synthesis we have achieved a related systematic literature review and meta-analysis. Accordingly, we have searched for relevant *open access* works, in 6 international databases: including [Cochrane](https://www.cochrane.org/)<sup>1</sup>, [Elsevier](https://www.elsevier.com/)<sup>2</sup>, [NCBI/PubMed](https://pubmed.ncbi.nlm.nih.gov/)<sup>3</sup>, [NCBI/PMC](https://www.ncbi.nlm.nih.gov/pmc/)<sup>4</sup>, [PEDro](https://pedro.org.au/)<sup>5</sup>, and [ISI Web of Knowledge/Science](https://apps.webofknowledge.com/WOS_GeneralSearch)<sup>6</sup>, published from January 2015 until December 2020. The contextually quested key words combinations/ syntaxes used in this respect were: "Pelotherapy /Peloidotherapy /Mud-therapy /Fango-therapy AND Rehabilitation".

The eligible articles were analyzed in detail regarding pathologies addressed by mud therapy/ rehabilitation – following a (Preferred Reporting Items for Systematic Reviews and Meta-Analyses – **PRISMA**<sup>7</sup> – type filter/ selection methodology – see Fig. 1) with additional country scientific relevance specified for this therapeutic method. The meta-analysis proceeded was designated to estimate the prevalence of various pathologies in the use of mud therapy/ rehabilitation.

#### **Inclusion and Exclusion Criteria**

Any relevant article that reported clinical or physical/chemical or biological information regarding peloids/mud therapy/ rehabilitation was included in the analysis. All articles with any design (reviews, randomized controlled trials, non-randomized controlled trials, case-control studies, cross-sectional studies), if eligible according to the above-mentioned selection methodology, were included.

Articles were excluded if they didn't reach – using a weighted, own, PEDro inspired scoring classification – at least a score of 4 – "fair quality" or more points.

#### **3. RESULTS**

Our search identified, first, **394** articles. Based on the successive filtering stages and, respectively, on the

<sup>1</sup> <https://www.cochrane.org/>

<sup>2</sup> <https://www.elsevier.com/>

<sup>3</sup> <https://pubmed.ncbi.nlm.nih.gov/>

<sup>4</sup> <https://www.ncbi.nlm.nih.gov/pmc/>

<sup>5</sup> <https://pedro.org.au/>

<sup>6</sup> [http://apps.webofknowledge.com/WOS\\_GeneralSearch](http://apps.webofknowledge.com/WOS_GeneralSearch)

<sup>7</sup> <http://www.prisma-statement.org/>



classification criteria of the Physiotherapy Evidence Database (PEDro), we finally identified/retained and analyzed **68** articles (see Fig. 1).

Although, in principle, a rigorous method – and we have followed the PRISMA type paradigm – there still might be some missing works of our related article selection. On the other hand, to augment/ consolidate our documentation base, we have used also **40** papers freely found in the literature, and even – aiming, too, at an as exhaustive knowledge underpinning as possible – derogatively, we have also considered some articles which, probably being very new, couldn't yet have reached the PEDro threshold score we have settled.

#### **Meta-analysis (80)**

Afferent with the final step, we have done also a related Meta-analysis, **26** studies were included in this step, which count **15123** human subjects in total. The smallest sample size was **32** and the largest was **6281**. The meta-analysis (80) investigated the beneficial effects of mud therapy on specific indicated diseases.

Our obtained **forest plot**, also known as a **blobbogram**, is a graphical display of estimated results from several scientific studies addressing the same question, along with the overall results. Sometimes trials are just looking at different concepts. Statistical heterogeneity is apparent only after the analysis of the results. Heterogeneity may be judged graphically (by looking at the forest plot) and be measured statistically. In a forest plot from the systematic review, the error bars for each trial include the summary result, which suggests that statistical heterogeneity is not a problem and that the message is a consistent one (fig 3). To determine whether significant heterogeneity exists, a P-value high for the  $\chi^2$  test of heterogeneity is good news because it suggests that the heterogeneity is insignificant and that one can go ahead and summarise the results (81).

#### **4. Relevant topical data regarding mud therapy in, Physical and Rehabilitation Medicine (PRM) and Balneology**

In vivo experimental models (82) based on murine osteoarthritis or rheumatoid arthritis, to establish the actions of Hévíz mineral water and mud, Hungary (83) or Jeju Magma-Seawater, Korea (82) – by a modern methodological approach using functional tests and morphological analysis – provided favorable Evidence-Based data of Complementary and Alternative Medicine effects of these natural therapeutic-rehabilitative factors, that can be observed clinically in OA patients, too. Articular diseases are the most frequent causes of chronic pain and related disability. For instance, rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and progressive structural joint damage. Osteoarthritis is a degenerative process of the articular cartilage associated with hypertrophic changes in the bone (84). The new insights in the pathogenesis of

osteoarthritis (OA) reveal the implications of adipocytokines. In the last years, balneological research was directed towards the study of specific inflammatory cytokines' involvement in musculoskeletal disorders. Correlations between peloid therapy and inflammatory pathways, at a molecular level, are established and new insights into the world of chondrocytes and osteoblasts are brought to light (85).

Peat obtained from Tae'an-gun, Chungcheongnam-do, Korea, can be considered as a therapeutic option for pain relief of knee OA patients. Although short-term peat intervention did not have significant effects on serum cartilage oligomeric matrix protein, long-term follow-up assessment using several parameters, including pain and OA biomarkers (86), is needed. The reduction in knee joint varus/valgus range of motion and the increase in gait velocity after peat intervention are meaningful results as effects of peat intervention on gait parameters (87).

Experts agree that the Spa therapies are effective in controlling the symptoms and objective signs of disease in patients with musculoskeletal disorders, as well as in ensuring a decrease in the recruitment of NSAIDs and analgesics (88).

The hormetic effects of balneotherapy are related to different factors. The main factor that is common to all types of mineral-medicinal waters and muds is heat.

The anti-aging properties of mud therapy (69) are an exciting concept for prevention and slowing the aging process throughout the entire body and other dermatological diseases. Therapeutic spas and baths offer an atmosphere of health and physical fitness by their chemical, thermal, mechanical, and endocrine actions. They also provide relaxation and stress relief. Mud therapy is effective individually or as a complement to other medical therapies. Recently, the concept of thermal mud therapy has been changing. During the aging process, endocrine changes result in a decline in endocrine function involving the responsiveness of tissues as well as reduced hormone secretion from peripheral glands. This is coupled with modifications in the central mechanisms controlling the temporal organization of hormone release, with a dampening of circadian hormonal and non-hormonal rhythms. Compared to younger individuals, healthy older individuals have alterations in body composition and a decline in functional status: decreased muscle mass, increased fat mass, and decreased strength. Even with healthy aging, there are changes in endocrine systems, including estrogen (menopause), testosterone (andropause), growth hormone/insulin-like growth factor-I axis (somatopause), hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-cortisol axis, and dehydro-epiandrosterone and its sulfate (adrenopause) (89).

H<sub>2</sub>S – which is also a biochemical component within the mud, as well as radon (90) – induces a wide range of

physiological responses such as blood pressure modulation, neuromodulator in the brain and within the vasculature, protective against ischemic reperfusion injury, and anti-inflammatory reactions (36). H<sub>2</sub>S is an endogenous gasotransmitter, and, as such, it can be absorbed by numerous routes; it can penetrate the skin and mucosae and can therefore act at the cell level both in the skin (29) and in internal organs. Organic components of muds were demonstrated to have biological effects contributing to the healing mechanisms, but their medical significance is not still fully understood (91).

Techirghiol sapropelic mud is one of the natural therapeutic factors of medical use in Romania, being represented by the deposit on the bottom of lake Techirghiol; it has been and still is a subject to ongoing medical research because of the need of its medical use for scientific evidence-based medicine (92). One of the interesting papers regarding Techirghiol mud's post-resorptive effects, refer to the plasmatic level variations of leptin show a different response depending on the balneal application type. Warm mud application leads to a significant decrease of the leptin level which translates into the remission of inflammation and rheumatic pain. Cold mud application as a contrasting therapy leads to an increase of the leptin values at the end of the treatment, an increase that is not statistically significant. The lack of leptin variation in the case of the group that underwent constant therapy is due to the thermoregulation function that is highly strained during the cold application, while the thermal comfort during baths neutral from a thermal point of view stabilizes the hypothalamus function and does not request major neuroendocrine answers. Recent data indicate that the hypothalamus is targeted by leptin actions, leptin which crosses the hematoencephalic barrier and interacts with the leptin receptor in the arcuate nucleus of the hypothalamus, thereby controlling the thyroid-stimulating hormone, the melanocyte-stimulating hormone, and gamma-aminobutyric acid, which will eventually modulate the metabolic answers of the body (93).

## 5. DISCUSSION

The use of mud by humans for medicinal and wellness purposes is most probably as old as mankind. Balneotherapy is an effective complementary approach in the management of several low-grade inflammations and stress-related pathologies, especially rheumatic and metabolic conditions. However, despite the demonstrated clinical and symptomatic benefits of these therapies, their role in modern medicine is still controversial, mainly because the biological mechanisms underlying these benefits have not yet been completely elucidated. In the context of these pathologies, further studies are necessary to clarify the mechanisms of effects involving the stress response and, consequently, its interaction with the inflammatory response (42).

Thermal muds have been used in many spas for the treatment of different diseases (medical uses) as well as to clean and beautify the skin, in different forms/wellness such as mud baths, masks, and cataplasms (94). DPSIR (Drivers-Pressures-State change-Impacts-Responses) (95) framework can be used also to analyze touristic activities, including mud uses, to identify a set of key indicators with weightings for health tourism destinations by using an advanced analytic hierarchy process (AHP) method, derived from the official, academic, and professional opinions of the experts (96).

Yet, in the literature, mineralogical and chemical compositions and the possible toxicity of the peloids (97) need to be investigated and compared with some limits to determine whether they have any health benefits and potential applications for peliotherapeutic treatments (26). On the other hand, the therapeutic Euganean thermal mud is a unique product of the Euganean Thermal District (Italy) that represents the largest and oldest thermal center in Europe (54). The application of the therapeutic mud, whose beneficial effects have been documented since Ancient Roman times, is recognized by the Italian Health System as a healing treatment for arthrorheumatic diseases. The beneficial mud is obtained by a specific maturation procedure that can be considered as an ancient biotechnological process. This process is now coded by a protocol to be followed to obtain the "Mature Mud AOC" certification. The mud maturation process begins when virgin clay, obtained from the lakes of Arquà Petrarca (Padova, Italy), is laid in open-air tanks or silos of the different thermal Spas, and maintained there for a period of at least two months, constantly covered by a layer of flowing thermal water, at the indicated temperature of 38–40 °C. This maturation procedure allows a microbial community, mainly represented by cyanobacteria, to grow on the mud surface. Microorganisms, embedded in a thick polysaccharidic matrix, generate a green biofilm that indicates the correct mud maturation. Before using the mud for therapies, this is mixed and put in tanks in which thermal water at nearly 60 °C is present, to reduce the natural microbial load and maintain the fluidity of the product (98).

Additionally, Techirghiol represents ancient golf of the Black Sea, with sapropelic mud extracted from the lake, associated with marine climatic characteristics in a combined heliomarin and thalassotherapy cures. In BRST are treated patients with a wide range of diseases, most of them with osteoarticular and neurological pathology, both adults and children. Yearly, in Balneal and Rehabilitation Sanatorium from Techirghiol, are admitted more than ten thousand patients. The patients are admitted for a period of 12 days up to 30 days and they receive complex rehabilitation treatment: hydro-kinetic-therapy in the salted water of the pool, alternated with warm mud baths or hot mud wrapping, or cold mud ointment, and then

swim in the lake, completed with massage, electrotherapy, and kinesiotherapy. All patients underwent an initial clinical examination and then the physician filled up a questionnaire, which includes personal data, information about the disease requiring admission if the patient has in the medical history any balneal treatment and what were the results, and finally the group of affections to which fit the existing symptoms (99).

Delivery of drugs on/into/through the skin enables either local or systemic actions and improvement of poor biopharmaceutics profiles of drugs administered via other administration paths, and becomes a useful strategy in situations in which other administration routes are not possible or inadvisable. Peloidotherapy is the topical administration of hot-muds or peloids, with optimal rheological and thermal properties composed of clay minerals and mineral-medicinal water aimed at treating arthro-rheumatic issues, bone-muscle traumatic damage, and dermatological pathologies. Most of the important properties attributed to clays for dermo-cosmetic applications are related to their surface properties (surface area, cation exchange capacity, layer charge, among others); rheological properties (thixotropy, rheopexy, viscosity, plasticity); and other physical and mechanical properties including particle size and shape, color, softness, opacity, reflectance, iridescence, and so on (21).

The paucity of evidence about cost-effectiveness and economic evaluation of conservative, non-pharmacological and non-surgical rehabilitative interventions for the range of lower limb musculoskeletal complaints is a concern for one found study (100).

Balneotherapy could be beneficial in treating patients suffering from low back pain, but there is still not enough quality scientific evidence (101).

Mud produces important beneficial effects including anti-inflammatory and anti-microbial activity which might explain in part the therapeutic properties of mud packs against chronic inflammatory skin disorders. Besides, treatment of keratinocytes with mud extract led to a significant increase of ATP levels as well as mRNA expression of genes involved in cell protection and longevity. The mud could serve as a natural anti-oxidant and moisturizing anti-aging agent with important cosmeceutical applications (34).

## Figures and tables

**TABLE 1 Step I: numerical search results.**

Articles	Keywords	Web of Science	Cochrane	Elsevier	PubMed	PMC	PEDro	Total
Articles found in the first phase	"Mud therapy"	44	1	7	69	41	15	177
	"Peloidotherapy"	13	4	2	7	5	0	31
	"Pelotherapy"	52	2	2	14	29	0	99
	"Fango therapy"	0	1	0	0	0	0	1
	"Mud therapy" + "rehabilitation"	11	1	5	20	21	0	58
	"Peloidotherapy" + "rehabilitation"	2	0	1	3	2	0	8
	"Pelotherapy" + "rehabilitation"	3	0	0	4	13	0	20
	"Fango therapy" + "rehabilitation"	0	0	0	0	0	0	0
	<b>TOTAL</b>	<b>125</b>	<b>9</b>	<b>17</b>	<b>117</b>	<b>111</b>	<b>15</b>	<b>394</b>

Kinesiotherapy (therapeutic exercises including stretching, isotonic, isometric, and isokinetic strengthening), is effective in improving pain, joint stiffness, functional mobility and muscle strength in patients with knee OA. There are new data that emphasize the efficiency of the combined effect of geotherapy with kinesiotherapy in reducing pain for patients with osteoarthritis (102).

## 6. Conclusions

This paper overviews the current state-of-the-art knowledge in the approach of peloidotherapy in rehabilitation, with a focal point on the therapeutic properties of peloids. Most of the thermal spas around the world recommend their mud baths or local mud cataplastm applications, as they recognize therapeutic results through their anti-inflammatory, analgesic, and antiseptic effects on musculoskeletal and dermatologic pathologies, which are increasingly supported by clinical trials (103). Guidelines and studies reviewed are recognizing the beneficial effects and mechanisms of action of mud therapy (12). Osteoarthritis is the most addressed pathology (104)(105).

The works we have evaluated show that almost half of the thereof included patients originate from Romania.

Our systematic review and meta-analysis have emphasized an additional, corollary, conclusion, too: the often connected/ synergistic, therapeutic, and rehabilitative effects of the balneary interventions (46), including mud procedures based, prove and strengthen the Romanian successfully paradigm of a unitary/ sole specialty: Physical and Rehabilitation Medicine & Balneology – and this is reflected also in the new focus and title of our publication "Balneo and PRM Research Journal".

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## 8. Acknowledgments

This study, being a systematic review, did not require written consent from the patients involved.

All authors have equally contributed to this article.

## 9. Declaration of interests

Authors declare no competing interests.



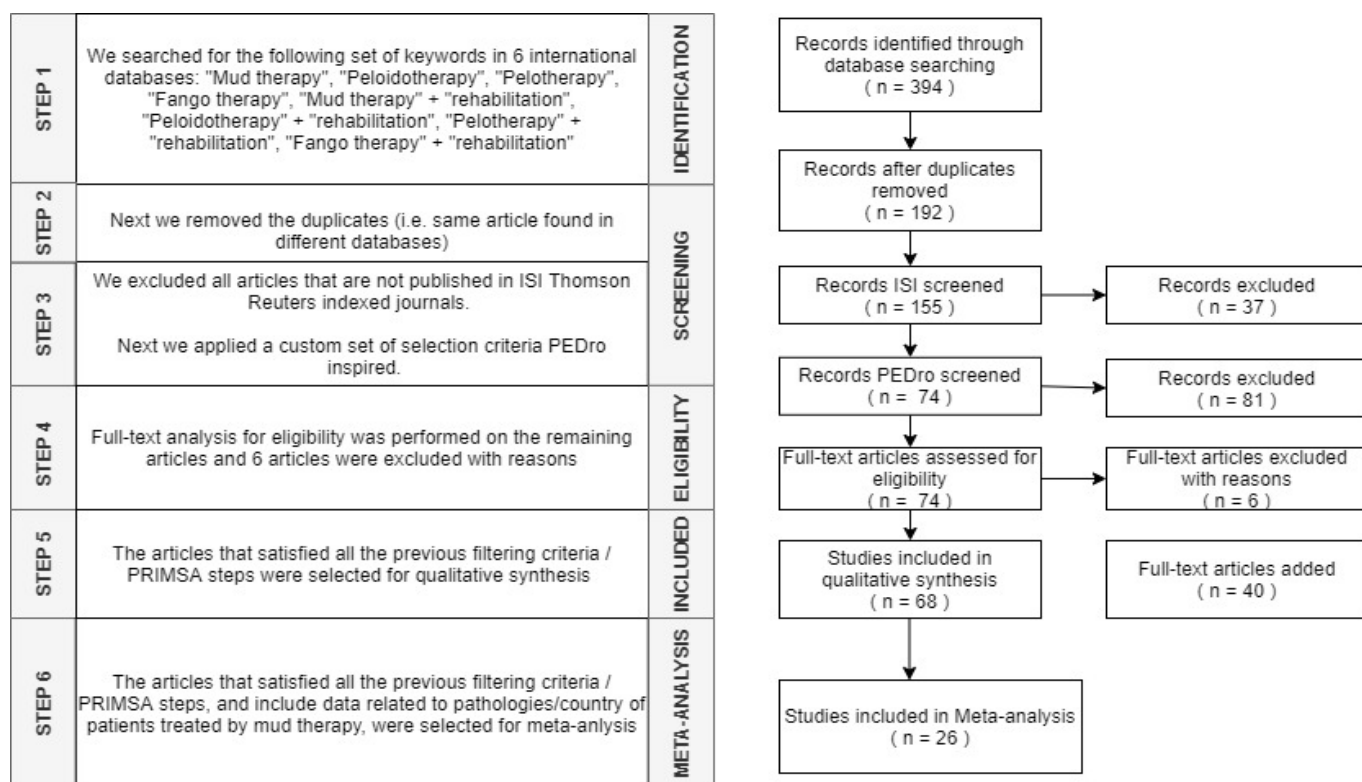


Figure 1: Flow-chart depicting the literature search and selection strategy. After applying the inclusion and exclusion criteria

TABLE 2 OpenMeta-Analyst source files related to pathologies/country patients treated by mud therapy

Study	Year	N - total patients	OA	Rheumatoid arthritis	Osteoporosis	Algic symptoms	Low Back Pain	Musculoskeletal disorders	Control	Romania	Spain	Hungary	Turkey	France	Italy	OTHER COUNTRY
<b>AXIS LEGEND</b>			<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
Karagülle (3)	2015	404	0	0	0	0	404	0	202	0	0	0	0	360	0	44
Morer (5)	2016	1118	599	308	64	0	147	0	535	0	0	397	156	0	0	721
Fioravanti (55)	2015	95	95	0	0	0	0	0	46	0	0	0	0	0	95	0
Fioravanti (106)	2015	103	53	0	0	0	0	0	50	0	0	0	0	0	103	0
Yücesoy (57)	2018	139	0	0	0	0	139	0	139	0	0	0	139	0	0	0
Forestier (58)	2016	2233	1721	0	0	0	0	0	512	0	132	117	330	642	378	634
Özkuk (32)	2017	50	50	0	0	0	0	0	50	0	0	0	50	0	0	0
Pascarelli (107)	2016	103	53	0	0	0	0	0	50	0	0	0	0	0	103	0
Eröksüz (70)	2019	50	0	0	0	0	0	50	50	0	0	0	50	0	0	0
Gungen (44)	2016	59	34	0	0	0	0	0	25	0	0	0	59	0	0	0
Valckenaere (108)	2018	185	0	0	0	92	0	0	93	0	0	0	0	185	0	0
Gyarmati (83)	2017	47	47	0	0	0	0	0	24	0	0	47	0	0	0	0
Tenti (31)	2020	212	212	0	0	0	0	0	212	0	0	0	0	0	212	0
Cantista (7)	2020	120	60	0	0	0	0	0	60	0	0	0	0	0	0	120
Alfier (102)	2020	48	48	24	0	0	0	0	24	0	0	0	0	0	0	48
Hahm (53)	2020	32	0	0	0	0	16	0	16	0	0	0	0	0	0	32
Aksoy (47)	2017	63	33	0	0	0	0	0	30	0	0	0	63	0	0	0
Kim (87)	2020	41	22	0	0	0	0	0	19	0	0	0	0	0	0	41
Ionescu (85)	2017	46	23	0	0	0	0	0	23	46	0	0	0	0	0	0
López (101)	2019	1390	0	0	0	0	1390	0	0	0	0	71	81	1192	0	46
Xiang (60)	2016	1010	1010	0	0	0	0	0	0	0	132	53	236	451	80	58
Gálvez (62)	2018	36	36	0	0	0	0	0	36	0	36	0	0	0	0	0
Iliescu (99)	2018	6281	2744	0	0	0	2273	0	0	6281	0	0	0	0	0	0
Varzaityte (65)	2019	92	32	0	0	0	0	0	60	0	0	0	0	0	0	92
Király (66)	2019	60	60	0	0	0	0	0	60	0	0	60	0	0	0	0
Hou (104)	2020	1106	440	0	0	0	0	0	411	0	121	53	151	451	290	50
<b>TOTAL</b>		<b>15123</b>	<b>7372</b>	<b>332</b>	<b>64</b>	<b>92</b>	<b>4369</b>	<b>50</b>	<b>2727</b>	<b>6327</b>	<b>421</b>	<b>798</b>	<b>1315</b>	<b>3281</b>	<b>1261</b>	<b>1886</b>
<b>%</b>		<b>100</b>	<b>48.75</b>	<b>2.20</b>	<b>0.42</b>	<b>0.61</b>	<b>28.89</b>	<b>0.33</b>	<b>18.03</b>	<b>41.84</b>	<b>2.78</b>	<b>5.28</b>	<b>8.70</b>	<b>21.70</b>	<b>8.34</b>	<b>12.47</b>

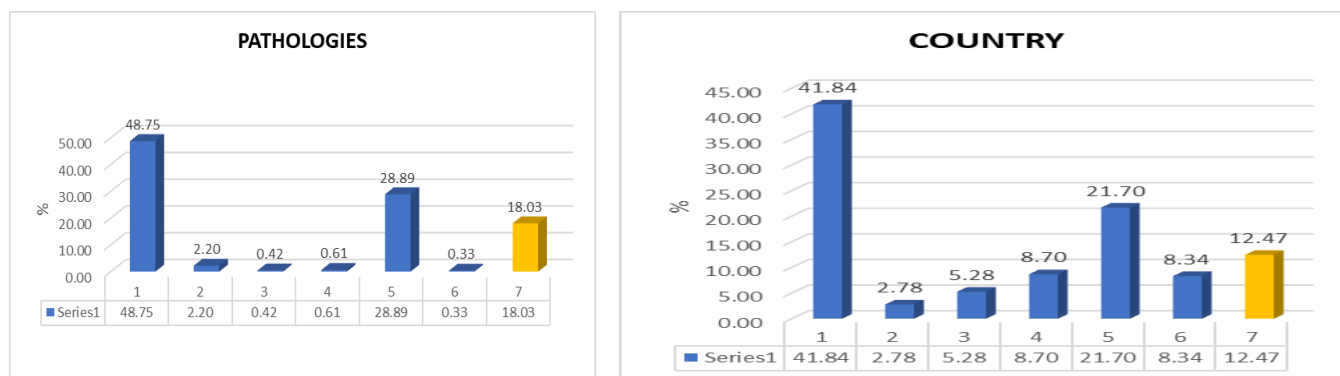


Figure 2: Pathologies and Country frequencies in mud therapy studies (see LEGEND in Table 3)

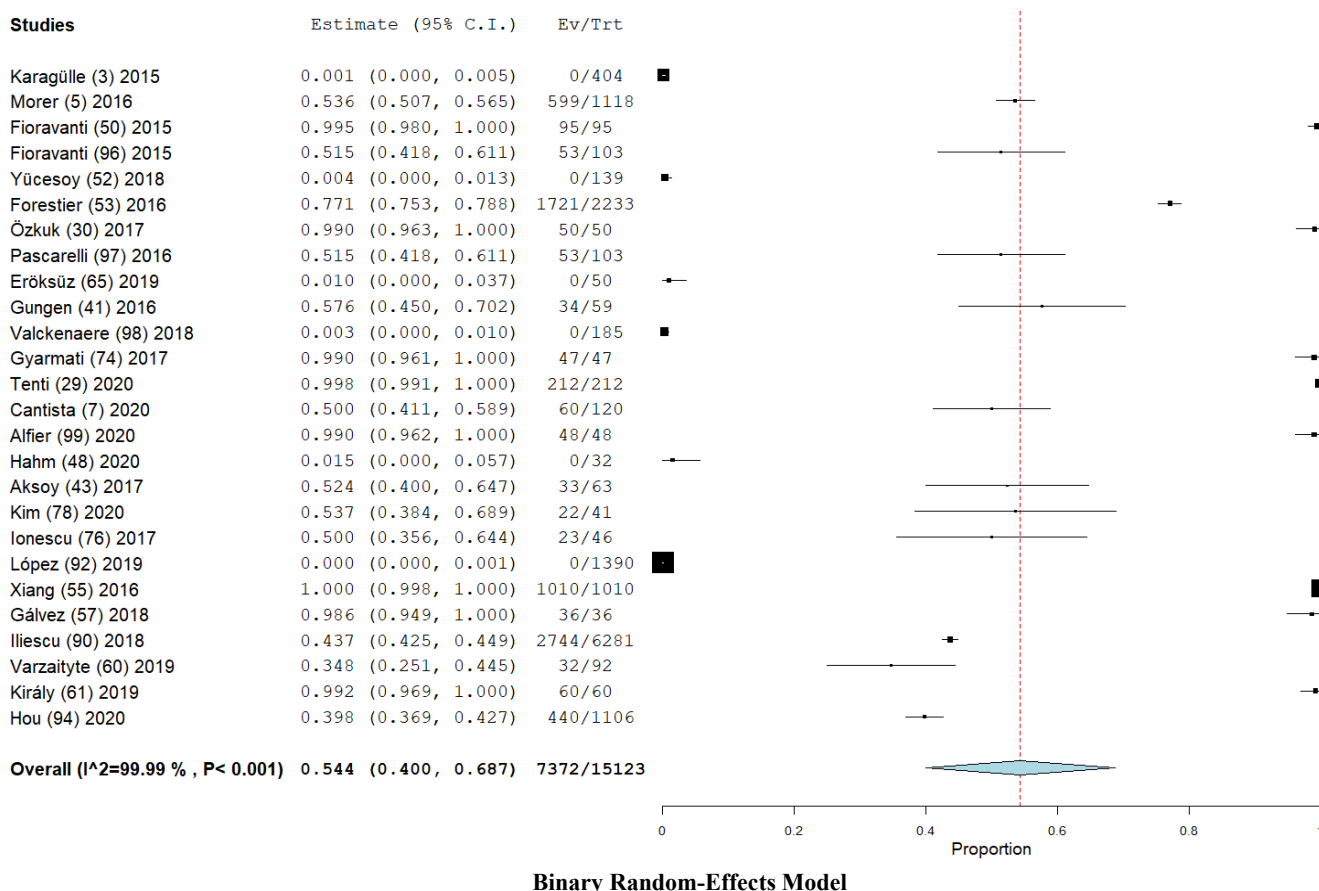


Figure 3: Studies Heterogeneity - forest-plot (80)

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## Appendix A. Supplementary data

No.	Source	Title	PEDro Score
1	PEDro	Karagülle M, Karagülle MZ. Effectiveness of balneotherapy and spa therapy for the treatment of chronic low back pain: a review on latest evidence. <i>Clin Rheumatol</i> . 2015;34(2):207–14.	10
2	NCBI/PMC	Dolbeth M, Stålnacke P, Alves FL, Sousa LP, Gooch GD, Khokhlov V, et al. An integrated Pan-European perspective on coastal Lagoons management through a mosaic-DPSIR approach. <i>Sci Rep</i> . 2016;6(March 2015):1–12.	10
3	NCBI/PMC	Zampieri RM, Adessi A, Caldara F, Codato A, Furlan M, Rampazzo C, et al. Anti-inflammatory activity of exopolysaccharides from <i>Phormidium</i> sp. ETS05, the most abundant cyanobacterium of the therapeutic euganean thermal muds, using the zebrafish model. <i>Biomolecules</i> . 2020;10(4).	10
4	NCBI/PMC	Masiero S, Maccarone MC, Magro G. Balneotherapy and human immune function in the era of COVID-19. <i>Int J Biometeorol</i> . 2020;64(8):1433–4.	10
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## Neuroplasticity pathophysiological mechanisms underlying neuro-optometric rehabilitation in ischemic stroke – a brief review



WEB OF SCIENCE

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### Abstract

Neuroplasticity is an essential phenomenon underlying on neurorehabilitation process, by which the brain can remodel the dysfunction consequent to a lesion. Ischemic brain lesions are the most frequent brain lesions often associated with visual function disability. Experimental and clinical studies established that visual function disability can impede the neurorehabilitation therapy efficiency. Neuro-optometric therapy has been proved to significantly improve the patient outcome after brain lesions. The pathophysiological mechanisms underlying this process are yet to be deciphered. Current knowledge regarding the pathophysiological mechanisms involved in ischemic lesions and neuroplasticity as a reparation process offers real support to a more efficient neurorehabilitation therapy that can contribute to the improvement of life quality in stroke patients.

**Keywords:** *neuroplasticity, neuro-optometric rehabilitation, ischemic stroke,*

### Introduction

The human brain has a large area designed for visual function consisting of two visual systems: one stream (ventral stream in the occipital cortex) vision for perception and one stream (dorsal stream in the parietal cortex) vision for action. The brain areas that control the visual information are at least 10 different specialized brain regions that are involved in controlling separate types of behavior regarding the guiding eyes and head movements towards an environmental object and adapt the body movement to the walking direction or even for a standing position (1). An important role in these actions is also played by subcortical structures such as pretectum and superior colliculus (2). There is another important factor that has to be taken into consideration represented by aging. Aging processes add ophthalmologic disorders such as lens opacities, age-related macular degeneration, or microangiopathic retinal vessel changes that can distort the image perception (3). Still, there is a specific individual variation of visual function pathophysiology that are orientated the practitioners to carefully assess each patient to indicate the most suitable individual treatment, according to individual clinical and paraclinical examination (4). This is specifically

indicated in the neurorehabilitation process since the brain lesions can be complex and with various functional consequences and disabilities. Together with exercise interventions balneological procedures and other neurorehabilitation therapy, neuro-optometric methods can contribute to more efficient neurorehabilitation in ischemic stroke patients (5-7).

Neuro-optometric treatment comprises all the methods addressed to visual disabilities (perception, processing, motor disabilities) resulting from visual system disorders. Since the brain activity is highly orientated on visual information processing starting with the cortical perception of visual information and transmitting process to the specialized networks, the brain neuroplasticity offers various opportunities to set a new point of functionality by therapeutic methods to improve the visual system disabilities after brain damage (8). Various visual disabilities resulting from brain lesions can be alleviated by neuro-optometric rehabilitation (9,10). These are represented by cranial nerve lesions that can lead to disabilities such as oculomotor imbalances resulting in acquired strabismus and diplopia, convergence/accommodation, paresis/paralysis,

visuospatial dysfunctions, visual perceptual, and intracranial optic pathways lesions (11). The three systems (visual, somatosensory, and vestibular systems) contribute to inputs that assure postural control and motor functions. None of these systems can provide alone the information needed for a precise motion and body position into the spatial environment. Consequently, the contribution of each system is essential and has a considerable effect on the outcome of the neurorehabilitation process. The visual system contributes to the orientation of the body in the space, assesses the position of the body and the spatiality of the objects around to transmit adequate information to the brain. The visual system function, after the ischemic stroke, is contributing essentially to prevent the patient to fall and, further, contribute to the motor coordination and movements into space (12). There is a degree of redundancy in the contribution of each system to postural balance. For a healthy subject, the visual system has more influence on the standing position for posture maintenance than the vestibular system (13). The vestibular system has more influence in moving, and stabilization of the body in the standing position (especially the head and the trunk) (14). In a healthy subject, visual system inputs can be balanced by vestibular function but the balance of the posture is more difficult (14). This evidence can be an important contributor to neurorehabilitation success. Opposite, the visual system can only partially compensate for the dysfunction of the vestibular system, the rehabilitation process being even slower in this instance (15).

#### **Neuroplasticity applied to neuro-optometric rehabilitation in ischemic stroke**

Perception is an essential process in vision function. The Eye-brain unit is unreplaceable for a perfect motor function commended by the cortex. Brain diseases that interfere with visual pathways can alter the optical perfect image. Neuroplasticity is the phenomenon of the brain's ability to reorganize the structure and molecular function to get new neural networks to ensure the response to environmental changes (16). Since visual function pathways are completely developed at the same time as the nervous system, the neuroplasticity phenomenon has to be addressed, in adult time, to a developed neural network. Despite the fact the classic concept of neuronal regeneration theorized the low capacity of neurons to regenerate, the new researches bring evidence of neural repair possibilities and a new generation of neuronal cell formation in adult life (17). The human brain possesses high capacities of neuroplasticity which has as a consequence the efficiency of the neuro-rehabilitation process. Since visual pathways are connected with a complex network with multiple cortical areas and are essential for various functions, brain plasticity can contribute to restoration at least

partially of impaired functions. Cerebral reorganization after stroke consists of the overactivation of healthy neurons, synapses, and neuronal networks that can substitute the functions of affected brain tissue. These activations are often bilateral, involving sensory-motor, premotor, parietal, prefrontal areas, brainstem, and cerebellum. The initial overactivation was demonstrated to be more intense in those patients with the greatest clinical deficit (18). Various non-invasive techniques to assess brain functions (functional magnetic resonance imaging, positron emission tomography, and brain stimulation with transcranial magnetic stimulation) bring new inside in the neurorehabilitation process and demonstrated the rehabilitation therapies efficiency (18). The impact of the revolution of science in neurorehabilitation as a basis for the neuroplasticity phenomenon and neural regeneration. Neurorehabilitation term was increased in scientific literature started with 1980, gradually accelerated in the last years. Application of basic science and evidence-based medicine on neurorehabilitation methods research improved their efficiency with significant benefit for the patients (19). Even the clear borders are yet not established, two types of neuroplasticity were studied: structural neuroplasticity and functional synaptic plasticity. The therapeutic manipulation of the neuroplasticity phenomenon relies on scientific studies starting from molecular levels of neuronal networks repair processes due to neurotransmitters and growth factors contribution and continued with clinical trials. Therefore, the achievements in the neurorehabilitation area are based on experimental studies designed to explore the anatomical and physiological pathophysiological substrate of the lesions induced by neuronal ischemia, with complex consequences on neuronal networks (20).

The neurorehabilitation process has to be addressed to repair methods due to the neuroplasticity process and to complete the best functional outcome. From the structural point of view, the brain has a lot of connections through synapses, building new connectivities even in normal conditions, to adapt to the environment and the daily tasks of the patient. Therefore, the brain is the proper organ where the plasticity phenomenon can exert and develop according to the new living condition or with the occurred lesions (21). Skill learning has previously demonstrated to imply the increase of synapses number and the synaptic activity, by the synthesis of a higher amount of neurotransmitters (22). To this synaptic plasticity, an increase of dendrites number is also added (22). According to the intensity of stimulation, the synaptic activity can be modulated and synapses efficiency can change, according to the new conditions (23,24). This extraordinary power of brain structure and function modulation can be very useful in the rehabilitation process for building new connectivities and

empowering synaptic functions to replace the disability induced by brain lesions. Pharmacological manipulation of synaptic activity can be also a method to reshape the functional brain map by synaptic plasticity (25). Both  $\gamma$ -aminobutyric acid (GABA) and glutamate (through NMDA and AMPA receptors) can contribute to the efficiency of synapsis, facilitation or inhibiting the synaptic activity to build new neural networks for a diminished or lost function (25,26). The precise correlation between synaptogenesis and neurotransmitters synthesis and the neuroplasticity phenomenon linked to the neurorehabilitation process has to be further established.

Neurorehabilitation is a complex process that involves a specialized team, working interdisciplinary and having as a target the best possible treatment addressed to recuperate the lost or diminished functions. Even the rehabilitation process is slow and the achievements are not the desired ones, the socio-economic impact of any grade of re functional recovery can be considerable. A complex condition related to the patient's disability has to be approached by different medical specialists to get the most efficient rehabilitation program. This paper aimed to facilitate a brief review of the main technics addressed to the contribution of neuro-optometric rehabilitation to the entire neurorehabilitation process, and, finally to the quality of life improving in stroke patients.

#### **Perceptual disorders and their rehabilitation**

Perceptual disorders are represented mainly by unilateral spatial neglect (USN), reported in about 25 % are commonly associated with right parietal lesions (7). Patients with USN have a slow progression of rehabilitation results and usually need assistance after discharge. The current knowledge from the literature review shows that the presence of USN is an independent predictor of the functional outcome being associated with poor rehabilitation results (27). There is no consensus about the efficiency or benefits of different rehabilitation-techniques, nor about the mechanisms that can constitute the substrate for the neuronal network of USN onset. Therefore, due to imprecise theories that explain the USN presence, the rehabilitation therapies' efficiency is only-related to different experiences and clinical studies of several researchers focused on this field. The understanding of the pathophysiology of USN will be strongly related to the development of more efficient neuro-rehabilitation therapies. Patients with USN demonstrated that hemi-intention is implied in daily living activities, their performances being lower than ischemic stroke patients without USN (28).

The performances of daily living activities are strongly correlated with somatosensorial, motor, and visual function status. Daily living activities such as dressing or walking are less affected than hygiene maneuvers, eating,

or using the telephone (28). Visual disability rehabilitation associated with USN can improve stroke patients' evolution and contribute to a better neurorehabilitation outcome (29). Small sample sizes are the main limitations in many published trials. Most of the published studies used stimulation of the direction of gaze towards the left, using top-down techniques where the patient has to follow the therapist's indications (30). According to Azouvi et al, there are four methods of USN rehabilitation, based on theoretical concepts that tried to explain the USN underlying mechanisms: enhance the attention of neglect behavior by top-down mechanisms; sensory stimulation by bottom-up methods; inhibitory processes modulation methods; arousal enhancement (29). All of the technics have no concerns of efficiency, but reported results are encouraging and since there is no optical rehabilitation therapy stated as a basis of visual recovery function, each study deserves attention and should be developed for new data collection. The interventions consisting of strategies addressed to the enhancement of the attention towards the neglected side stimulus, correcting the body position to better visualization of the stimulus, spatial representation of the patients to improve visual field and a to increase awareness to the visual stimulus, optometric corrections with prisms, eyepatching, hemispatial glasses, caloric stimulation could be valuable methods to improve the patient attention and finally neurologic rehabilitation. The efforts made in this direction are focused on better neurological rehabilitation after ischemic stroke, and improvement of USN condition by visual function recovery could be a valuable helpful step.

One of the most used optometric technics consists in the modulation of spatial cognition by prism correction therapy. Most of the programs include one or two daily prisms optometric treatment, during the day – usually during the functional activities (over 2 weeks period) (31,32). The technique consists of three steps (31,32):

- assessing the patient's visual abilities without prisms (basal assessment); this step offers the reference values that need to be compared with after therapy visual outcome.

- prism prescription ( the prisms has to deviate the environment with 10° to the right); the patients will gradually improve his error, after the prisms treatment

- assessment of the visual abilities to follow the visual target after the prisms treatment.

This simple non-invasive period has the advantages to improve spatial neglect by manipulating the plasticity of sensory-motor cortical networks through activation of associative cortical regions (during the prism treatment). There are no demonstrated effects following exposure to the prism treatment towards the left, therefore there is a specificity of this treatment that is direction-dependent

(33). Therefore, prisms treatment is a promising treatment in neurorehabilitation therapy via the improvement of the visuomotor system. Adaptive neuroplasticity changes produced by prisms exposure, balancing the ischemic damages produced by brain hypoperfusion and ischemia. Frontal and parietal structures involved in these dysfunctions and consequently hemispatial neglect will undergo plasticity phenomenon and the molecular mechanism based on this phenomenon has to be still investigated (34). Improving the spatial neglect after prisms therapy proves the neuroplasticity ability to contribute to new neuronal network formation that is responsible to recuperate the lost functions after brain injury (35,36).

### **Sensory disabilities due to cerebral blindness**

The pathophysiology of sensory disabilities is depending on permanency or temporarily visual disabilities. If light deprivation or cerebral blindness is permanent, is followed by the inability to avoid obstacles, tracking moving objects, optokinetic nystagmus, visuomotor behavior changes. Cerebral blindness is defined as bilateral vision loss, secondary to interruption on visual pathways, posterior to lateral geniculate nuclei (37). Cortical blindness (as a part of cerebral blindness) refers to the loss of vision without any ophthalmological diseases and with normal pupillary light reflexes due to bilateral lesions of the occipital cortex (38). Stroke and other causes can cause cerebral blindness. The most common causes that can produce cerebral blindness, besides stroke are represented by occipital lobe epilepsy, hyponatremia, severe hypoglycemia, vasculitis, hypertensive encephalopathy, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes). Some of these etiologies can be reversible (39). The ophthalmoscopic examination reveals no abnormalities. The pupillary light reflex can be impaired, depending on the etiology of sensory disability (40). All visual sensorial parameters such as visual acuity, visual field, contrast sensitivity can be altered according to the topography of the lesions. Still, the human brain of patients with cerebral blindness possesses remarkable behavioral and neuroanatomical, and functional compensatory mechanisms for visual disabilities improvement, based on brain plasticity (41).

### **Conclusions**

The effectiveness of neurorehabilitation methods could be improved by adding an important contributing element such as visual rehabilitation. Visual rehabilitation in stroke patients has as an important underlying process represented by brain plasticity. Functional augmentation can be achieved either by specific visual therapies or pharmacological methods addressed to improve synaptic activity and new neuronal network building and consolidation. New clinical studies that can describe the pathological mechanisms associated with visual

disabilities after cerebral ischemia could be specifically useful to improve the life quality for stroke patients.

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## Modern views on the role and place of gerontological rehabilitation in the nation's health improvement system



WEB OF SCIENCE

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### Abstract

The article discusses the aging process (theory of aging, mechanism, concept of the aging process, physiological and functional changes that negatively affect the condition of a patient with a gerontological profile). Geriatric rehabilitation is discussed, including physical (professional geriatric rehabilitation based on rehabilitation centers) and mental rehabilitation. It is shown that medical and psychological rehabilitation, which includes psychocorrection and psychotherapy, is essential. The paper assesses the rehabilitation possibilities (rehabilitation algorithms involving both natural and preformed physical factors) in gerontological patients suffering from various somatic diseases

**Keywords:** *aging, geriatric rehabilitation, medical and physical rehabilitation, medical and psychological rehabilitation,*

### Introduction

One of the urgent social, medical, political, demographic problems of modern society's life is a significant increase in the life expectancy of a person. The average life expectancy globally is 72 years (70 for men and 75 for women (1, 2, 3). In Ukraine, the average life expectancy is 71.98 years. Still, the total life expectancy in Ukraine is significantly lower than in social and economically developed countries of western Europe, where it is 80.3 years (4). Aging is a polyetiological process caused by genetically determined metabolic characteristics, diseases, an increase in the number of free radicals, the accumulation of nitrogen compounds, lipid peroxide products, xenobiotics, hypoxia, etc. Modern medical science pays excellent attention to the problem of aging; the emergence of new facts allows a deeper understanding of the mechanisms of this process. Today there are several theories of aging, which partly contradict each other, and partly supplement.

The most famous concepts of aging today are an accumulation of mutations, hormonal and genetic; mitochondrial; epigenetic; free radicals, somatic mutations; evolutionary-genetic, etc. (5, 6, 7, 8, 9).

To better understand of the aging process, it should be noted that aging begins at the moment of conception and continues until the end of life. The stages of aging of the organism reflect the organism's genetically determined ability to adapt and compensate for losses from

pathological processes. With age, all body systems show a decrease in performance. Today it is customary to divide the aging process into several periods conventionally: early - from 68 to 74 years old) middle - from 75 to 84 years; and later - over 95 years old.

With age, there is a decrease in functional systems' performance of; that is, people are less able to withstand external influences and changes in internal needs. Human aging is assessed by a spectrum of physiological changes that contribute to the death's risk by reducing the functional systems' activity, which makes the body more susceptible to many diseases (10). Population aging in terms of demographic mortality rates is growing exponentially (11, 12). The decrease in the capabilities of human functional systems with age tends to a linear relationship and is characterized by gradual changes, such as:

- decrease in height and weight due to loss of muscle and bone mass;
- slowdown and changes in metabolism
- an increase in the time for the implementation of reactions;
- decreased memory functions;
- deterioration of kidney function
- suppression of immune function;
- decrease in physical performance;
- numerous endocrine changes.

The above features of structural and physiological changes in the body of the elderly or senile age make it necessary to consider when developing rehabilitation measures to restore the state after a disease, and form a particular section of rehabilitation - geriatric rehabilitation. (13). Geriatric rehabilitation is understood as a set of measures aimed at maintaining independence, improving the quality of life and emotional well-being (14, 15). The goal of geriatric rehabilitation is to reactivate, resocialize, and reintegrate the patient.

Reactivation - measures aimed at restoring physically and socially inactive people's activity, increasing daily activity in their environment.

Resocialization - measures aimed at restoring contact with the family and getting out of isolation.

Reintegration is the return of an older person to society.

One of the areas of geriatric rehabilitation is medical rehabilitation, which includes physical and psychological rehabilitation. In turn, physical rehabilitation consists of remedial gymnastics, occupational therapy, physiotherapy, etc. The most accessible for older people are light physical exercises, which include: morning exercises, remedial gymnastics, industrial gymnastics, dosed use of elements of outdoor games and sports.

Physiotherapy is one of the most effective areas of rehabilitation therapy. Physical therapy under the guidance of a physician or methodologist can treat almost all chronic diseases. However, an indispensable condition, is a correct dosage, strict consideration of both the patient's well-being and objective indicators of the body's systems' functional state, primarily the cardiovascular system.

Massage is another type of physical rehabilitation for the elderly. The most widely used therapeutic and hygienic massage, most often in combination with physiotherapy exercises.

Psychological rehabilitation is made up of both drug methods and various types of psychotherapy.

Gerontological care includes three areas: diagnosis, interventions, outcomes. Social rehabilitation means resocialization, that is, the return of the elderly to society, overcoming their isolation, social activity of the elderly and older people and expanding of their social contacts. For this purpose, both traditional sources of assistance (state social assistance systems) and informal sources are used - family members, friends, neighbors, voluntary and charitable organizations (16). An essential part of social rehabilitation is spiritual rehabilitation, the meaning of which is to provide spiritual support to the elderly.

Educational geriatric rehabilitation is an introduction to older people about the processes taking place in their body, about the possibility of self-help, and sources of support. This impacts the older person in the direction of increasing his confidence in his abilities through the

acquisition of new experience and new knowledge. The mass media are of great importance, as they can raise older people's educational level, inform about the general problems associated with aging, and form a positive image of older people in society.

Professional geriatric rehabilitation includes maintaining more prolonged possible working capacity, organizing a retraining system of and training for the elderly based on rehabilitation centers, providing jobs for the elderly, and involving pensioners as widely as possible in socially significant activities (15, 16).

It should be noted that this division into types is rather arbitrary: the individual components are interrelated and complement each other. The ultimate goal of all these activities is to restore independence in physical, mental, social, and professional relationships and improve older people's quality of life and well-being of.

In terms of duration, geriatric rehabilitation is carried out: in acute conditions, in subacute conditions, and long-term.

Basic principles of rehabilitation of elderly people

1. Early initiation of rehabilitation measures, which should complement and enrich the main therapy.
2. Stages of rehabilitation.
3. Continuity and continuity of rehabilitation measures as one of the basic and mandatory conditions for the effectiveness of treatment.
4. The complex nature of rehabilitation.
5. An individual approach to the preparation of rehabilitation programs. An individual profile must be established for each patient.
6. Risk factors, physical and mental characteristics, emotional reactions to the disease.

At each stage of rehabilitation, a program is drawn up, to identify the reserve capabilities of the body and help the patient achieve a high level of working condition. The psychological component includes studies of psychophysiology, intellectual and anamnestic characteristics, and the system older people's relations to restore, maintain and correct them. It is also expected to work with the family of patients. The principles of psychocorrectional work include the following:

- group approach;
- improved mood;
- reducing anxiety;
- increased self-esteem;
- the possibility of self-realization;
- the motivation for social activity, improving communication skills;
- adaptation up to date.

Considering the the elderly and senile age's psychological characteristics, the preference is given to group forms of work. Psychological rehabilitation for any somatic disease is aimed at different levels of the patient's mental

organization and psychological components included in the etiopathogenesis of the disease.

1. Influence on the neurotic component of a somatic disease (functional and dynamic changes accompany all somatic diseases).
2. Influence on the mental component of a complex of etiological factors.
3. Influence on the patient's personality to change his reaction to the disease, correct the "scale of the experience of the disease", to improve its functioning in the new conditions of somatic disease.

Traditionally, much attention is paid to the diagnosis and correction of cognitive processes in the elderly. The socio-economic component affects aspects of lifestyle changes. The professional component aims to restore production skills impaired due to injury or illness; in case of loss of professional ability to work - stable or partial - the patient can be prepared to learn a new profession. As for medical rehabilitation, it is carried out both using traditional medicine and by alternative means. The latter includes physiotherapy exercises, physiotherapy, occupational therapy and household rehabilitation, diet therapy, phytotherapy, reflexology, manual therapy, aromatherapy, bioresonance therapy, psychotherapy, and psychocorrection.

When prescribing physical methods of treatment, it is necessary to consider the characteristics of the aging organism and, first of all, the cardiovascular system, changes in its reactivity. Before the appointment of hardware physiotherapy and balneological procedures, a thorough clinical examination should be carried out, including studying of the function of the cardiovascular system. It should be borne in mind that any types of treatment by physical methods exert not only local but also general effects through the central nervous system, often require the mobilization of significant reserves, which the body of an elderly and especially an older person, as a rule, does not have. Great care should be taken with all types of hydrotherapy, although most elderly patients tolerate coniferous, iodine-bromine, oxygen baths, worse carbonic baths. And also, underwater massage is quite a big load for the elderly.

Thermal irritants in the elderly and older people cause feeble and delayed compensatory reactions of the skin capillaries. They are often inadequate and even paradoxical, and in response to the action of a thermal stimulus, not expansion but narrowing of the peripheral vascular network is observed. As a rule, drug electrophoresis, ultrasound treatment with the introduction of drugs through the skin, local application of UHF therapy, Bernard currents (diadynamic) in reduced doses are well tolerated. As an equivalent of a course treatment with injections of a 2% solution of novocaine, introducing of a 5% solution of novocaine by electrophoresis (from the positive pole) can be

recommended. The method of choice is magnetotherapy, one of the most favorable and fairly easily tolerated methods of physical treatment against the background of natural physiotherapeutic factors (17).

Physical therapy methods play an essential role in preventing premature aging and treating of diseases, especially during the rehabilitation period. While the usual ways of drug therapy and rehabilitation often lead to the development of intoxication, allergic reactions, methods of physical rehabilitation, as a rule, allow avoiding this danger (18).

The following features of rehabilitation in geriatrics have been identified:

- the processes of readaptation in old age are slower; therefore, rehabilitation requires more time.
- compensatory opportunities are limited; therefore, rehabilitation programs must be adequate.
- an advantage in the rehabilitation of the elderly is given to non-drug types of a restorative treatment since intoxication and allergization develop faster with age.

Along with traditional methods of physiotherapy, magnetic field treatment, thermal therapy, hydrotherapy, classical massage, physiotherapy exercises, the rehabilitation program includes occupational therapy, group and individual forms of psychocorrection, and psychotherapy (19).

Occupational therapy is an active method of restoring and compensating for impaired functions through various work to create a useful product. In occupational therapy, the affected systems' very process of functioning acts as a therapeutic and restorative factor (20). According to the main tasks, means, and methods, the following occupational therapy types of are distinguished.

Reinforcing occupational therapy is a means of increasing the patient's general vitality and creates the psychological prerequisites for readaptation.

Household occupational therapy. It is carried out with patients who have suffered from acute cerebrovascular accidents, aggravated by paresis of varying severity, and patients who have senile dementia. Household rehabilitation should be started as early as possible since its goal is to eliminate the helplessness of the patient through sequential training in various activities, differentiated in complexity, in the field of self-care.

Rehabilitation occupational therapy impacts on the damaged part of the body, organ, or system to restore the function disturbed by the pathological process with appropriately selected types of labor activity.

Recreational occupational therapy - reducing the severity of aggravating factors caused by the forced extended stay in bed or a medical institution. It has a wide variety of forms, can be both entertaining and educational. The method's attractiveness is in the ease of use and low material costs in the organization; availability of use at all stages of rehabilitation.



Physiotherapy exercises are central to the physical rehabilitation of the elderly as the most biologically based method of treatment. Regular exercise has a positive effect on the work of all organs and systems. The cardiovascular system has great reserve capabilities, due to which the risk of cardiovascular diseases is reduced. Respiratory system - more active use of oxygen by body tissues, slowing down the processes of reducing lung tissue elasticity. Metabolism - the content of cholesterol and triglycerides in the blood changes for the better. Mental sphere - activation of mental activity; beneficial effect on mood; reducing anxiety and increasing interest in the world. Maintaining independence in everyday life depends primarily on mobility, which is determined by the performance of muscles, bones, and joints. Physical exercise will help develop strength, flexibility, endurance, which is vital for a person leading an independent lifestyle.

Physiotherapy is the practice of geriatrics is becoming important. At present, many author's complexes and programs of physical exercises of a health-improving orientation have been developed and practically tested, which are intended for widespread use. Their main advantages are availability, ease of implementation, and efficiency. These are, first of all: controlled running loads (Cooper system), 1000 movements (Amosov system), 10,000 steps per day (Ikai system), running for life (Lidyard system). (21, 22, 23).

The most common exercises are walking, walking. Habitual physiological exercises are the best loads that a person can cope with more easily. It would help you if you started with walking (Scandinavian or straightforward), where there are multidirectional movements of the arms and legs, and it is necessary to control the pulse. The calculation formula is universal - 220 minus age. The pulse must be measured not only before, during, but also after the session. It is normal if the heart rate dropped 5 minutes after exercise approaching the initial value.

The health-improving effect of physical exercise is observed when it is rationally balanced by the capabilities of the patient. The systematic result of adequate physical activity on the human body leads to structural and functional restructuring, characterized by some psychological and physiological effects. Regular use of physical exercises and hardening factors increases the vitality of the body and natural immunity, improves the functions of the autonomic systems, efficiency and prevents premature aging.

In a complex of gymnastic exercises for the elderly, it is most useful to first perform gymnastics for the neck, which improves blood circulation in the brain stem. Therefore, local hypodynamia of the cervical spine is unfavorable for this category of patients (24). In atherosclerosis, the vessels lose their elasticity, become

stiff, and are difficult to adapt blood pressure fluctuations(25).

It is tough for many people who are still not old, to bend over, wash the bathtub, pick up a fallen object from the floor and get something from a low bedside table. This is due to limitations in the flexibility of the spine. Subsequently, limited joint mobility can cause the development of one or another orthopedic disease. Therefore, every day, regardless of age, it is necessary to perform exercises that will help develop and maintain joint mobility and thereby help prevent the development of pathological processes in them. These exercises should be performed before the onset of mild fatigue, increasing the number of repetitions and range of motion from session to session.

In addition to complexes of physical exercises in the doctors' arsenal of from rehabilitation medicine, there are also various massage, mechanotherapy, preformed and natural physical factors (26).

In geriathria, an integrative approach to palliative care is essential. Palliative care for the elderly should include specialized services and organizations. To work with this special group of patients, specialists who have received appropriate training are needed (27).

Psychocorrection and psychotherapy are important components of medical and psychological rehabilitation, aimed at full or partial restoration of the patient's personal and social status. Group forms of psychotherapy are the most appropriate method of psychological rehabilitation. Group psychotherapy, more than any other psychosocial influence method, contributes to the restoration of the system of relations between elderly patients with the microsocial environment, bringing value orientations following the way of life. There are two types of group methods of psychotherapy and sociotherapy in rehabilitation.

1. Therapeutic procedures aimed at the patient's social behavior, communication skills, self-realization, solving psychological problems and overcoming social conflicts.
2. The optimal is the organization of group of patients' social structure, based on the so-called environmental groups: functional groups, patients' club. These socio-therapeutic groups are focused on the social activation of patients and their involvement in society, promote communication training and instill in patients good behavior skills. They provide a corrective social climate to relive interpersonal relationships.

Relaxation techniques. Relaxation refers to the state of wakefulness, characterized by a decrease in psychophysiological activity, manifested in the whole organism or any of its systems. The clinical application of relaxation techniques has proven to be very useful in the treating of excessive stress and its clinical manifestations. The constant practical application of relaxation techniques can help reduce general anxiety.

Behavioral therapy is a treatment that uses teaching principles to change behavior and thinking. Behavioral therapy is based on a psychological model of social learning and a commitment to the scientific method. Terence Wilson highlights the following provisions in this regard (28).

1. Many cases of pathological behavior, from the point of view of behavioral therapy, are non-pathological “life problems”. These include, first of all, anxiety reactions, sexual deviations, behavior disorders.
2. Pathological behavior is mostly acquired and maintained in the same ways as normal behavior.
3. Behavioral diagnostics focuses more on the determinants of real behavior than on past life analysis. A person can be better understood, described, and evaluated by what he does in a particular situation.
4. Therapy requires a preliminary analysis of the problem, the allocation of individual components in it. These specific components are then systematically exposed to behavioral procedures.
5. Treatment strategies are developed individually for different problems in different individuals.
6. Understanding the origin of the psychological problem is irrelevant for implementing of behavioral changes; success in behavior change does not imply knowledge of its etiology.

Behavioral therapy is based on a scientific approach. This means that it starts from a clear conceptual framework that can be tested experimentally; treatment is consistent with the content and method of experimental clinical psychology; the technologies used can be described with sufficient accuracy to be measured objectively or to be replicated; therapeutic methods and concepts can be evaluated experimentally. Behavioral therapy seeks to provide the patient with a so-called “remedial learning experience”. This learning experience involves the acquiring of new behavioral strategies, increasing communicative competence, overcoming maladaptive stereotypes and destructive emotional conflicts.

And, finally, the sanatorium-resort stage, the issues of this treatment are always resolved individually. Sometimes, after a thorough examination, the patient is sent to the resort even with contraindications to use the main therapeutic factor of the resort to use other healing effects. For example, this resort's hydrogen sulfide baths are contraindicated for a patient, but climatotherapy is not contraindicated. An essential difference in geriatric rehabilitation is the constant need to restore lost functions, the formation of optimism, getting it out of depression, and restoring status in the family, work, and society. The well-established idea of the possibility of sending people over 60 for rest and treatment only to resorts near their place of residence, the inadmissibility of using the methods of intensive balneotherapy, although it

remains in force, in many cases no longer satisfies either the doctor or the patient.

This applies mainly to persons under the age of 65-70 with chronic diseases for which the most effective therapy can often be carried out in resorts, the climate of which is different from the local one and requires adaptation. Before deciding to send an older person to a spa treatment, it is necessary to conduct an extensive particularly thorough clinical study using various functional diagnostics methods and correctly assess the functional capabilities of the body.

Meteopathology - the study of adverse reactions of the body associated with changes in climatic and weather factors, is one of essential sections of climatology, is of particular importance in geriatric practice. The frequency of meteopathic reactions in humans increases significantly with aging. This explains why so many elderly and senile people develop meteorological stability.

Rehabilitation care is an important and integral part of the therapeutic process of treating gerontological patients. Therefore, the organization of rehabilitation moments for patients with a gerontological profile is one of the most challenging and still unresolved problems.

**Conclusions.** The relevance of gerontological patients' rehabilitation is mostly due to the need to expand the measures and capabilities of gerontological rehabilitation itself, which is based on physiological and functional changes in the state of health of patients. A multidisciplinary conceptual approach is needed - the combined use of factors of rehabilitation medicine in gerontological patients.

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## Improving functional and motor capacity through means/resources and methods specific to aquatic activities



WEB OF SCIENCE

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### Abstract

**Introduction.** Exercise programs in the aquatic environment have as their main objective the improvement and maintenance of physical capacity/ capability, these being in continuous development and diversification. Water exercise amplifies the effects of general physical exercise, by allowing a more precise control over the movement of each body segment and of the body as a whole. The aquatic environment offers a number of beneficial effects compared to ones offered by the terrestrial environment. The benefits obtained through the aquatic activities are fundamental and are reflected throughout the entire body including both motor, functional and aesthetic level. **Material and method.** The objective of this study is represented by the identification of new forms of physical exercise that will increase the effort's capacity. In order to achieve this goal, several methodological requirements were met, such as: successive engagement of the joints and muscle groups in effort (starting with the neck's muscles, shoulders, arms, torso and legs, simultaneously with scapular-humeral joints, spine and coxo-femoral joints and legs), the gradually usage of exercises, starting with the most basic and then increasing the complexity of the exercises, the usage of the accessible exercises in the beginning of the training, executed with high amplitude and reduced speed, focusing on the correctness of the execution, the selection and the adequate/ appropriately usage of the initial positions according to the subject's particularities and the shape/form of the exercise, the optimal control of the effort, achieved through a number of iterations, optimal execution time and breaks, the sets of general physical exercises will consist of sets of 8-12 exercises/reps, the principle of symmetry in the execution of the exercises has to be respected, the continuity of practicing a set of exercises for 6 to 8 consecutive lessons, the recommended work method is fragmented-imitative, efficiently combining the explication with the demonstration, the number of repetitions and the movement's correction. **Results and discussions.** Analyzing results obtained after the evaluation, we have noticed significant growth in the functional and motor capacities. **Conclusions.** The systematization of water activities on objective criteria effectively contributes to their knowledge, while allowing them to be included in the spectrum of recreational, sporting, relaxing or therapeutic activities.

**Keywords:** *aquatic activities, physical exercise, evaluations,*

### Introduction

The aquatic environment offers a number of opportunities compared to the terrestrial one [1,2]. The benefits obtained from performing aquatic activities are fundamental and are reflected on the whole body both motor, functional and aesthetic [8,11].

Effort capacity is defined as the ability of an organism to produce as much mechanical work as possible and to maintain it for as long as possible. In other words, the more effort a person can sustain in terms of intensity and duration, the better his capacity for effort is. The improvement of this parameter can be achieved through training, this being in fact, along with the series of technical-tactical skills, the final goal of the training process on which sports performance depends directly [6,7].

The aims of the study is improve somatic parameters, functional and motor capacity by implementing exercise programs performed in water by people aged between 40

and 55 years. In establishing the hypothesis we started from the assumption that performing water activities by people aged between 40 and 55, will improve their motor and functional capacity, compared to activities in the terrestrial environment (physiotherapy room) [9].

General objectives:

- ☐ improving somatic parameters;
- ☐ improving functional capacity;
- ☐ achieving an optimal psycho-physical balance;
- ☐ awareness of the advantages and characteristics of performing activities in the aquatic environment;
- ☐ diversification of exercise programs [10].

The stages of this research focused on the following aspects:

- ☐ establishing study groups;
- ☐ periodizing the research and establishing the conditions for conducting the study;
- ☐ establishing specific training objectives;



- selecting and elaborating the means of action specific to aquatic activities;
- elaboration of aquagym programs on difficulty levels;
- establishing evaluation tools and rules [13].

## Material and Methods

The study was conducted over a period of 3 months, and consisted of 3 sessions per week, with a duration of 50 minutes.

The research included a number of 45 subjects, organized in three groups: two experimental groups and a control group. The experimental groups were formed each of 15 subjects aged between 40-45 years, as follows [12]:

- the first experiment group (E1), consisting of subjects, who performed a specific program of aquagym exercises;
- the second experiment group (E2), consisting of patients who practiced a specific program of aquagym exercises using various devices such as dumbbells or steppers.
- The control group (C) consisted of patients aged between 40 and 55 years who performed ground exercise programs.

The research included two tests, a initial test and a final test, arranged as follows:

- initial testing
- implementation of the proposed programs of aquatic activities and those in the gym
- final testing

Aquagym operational programs were differentiated on three levels: beginner, intermediate and advanced, depending on the degree of difficulty, intensity and complexity of the drive systems [4]. Measurements and tests applied in research: tests to determine the development of functional capacity: Ruffier test and walking test 2 Km [3].

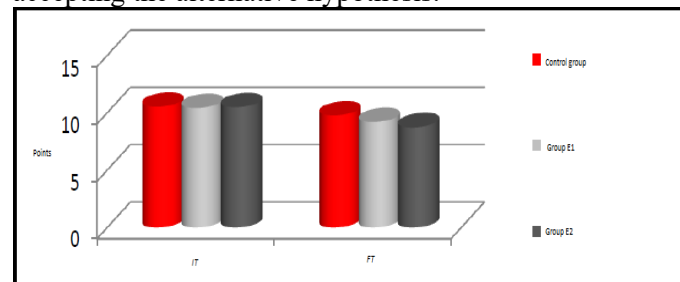
## Results and Discussion

**Effort capacity - Ruffier test.** Starting from approximately similar values at the initial test, after practicing the programs proposed the following differences of the arithmetic means between the two tests were obtained: 0.76 in the control group, 1.23 in the E1-Aquagym experiment group, and the E2-Aquagym experiment group - 1.75.

Reporting the values of the averages to the evaluation grid, it is found that at the initial testing all the groups included in the research were at a satisfactory level, with values between 10.1 -15, and after performing the proposed programs, in the final testing they registered an obvious progress, falling to the average level, with values below 10.

The analysis performed with the t-Student test is statistically significant for the E1-Aquagym experiment group compared to the control group, in the case of the E2-Aquagym experiment group, comparing the averages

with those of the control group, the statistical analysis indicates a strongly significant difference,  $p < 0.000$ , thus accepting the alternative hypothesis.

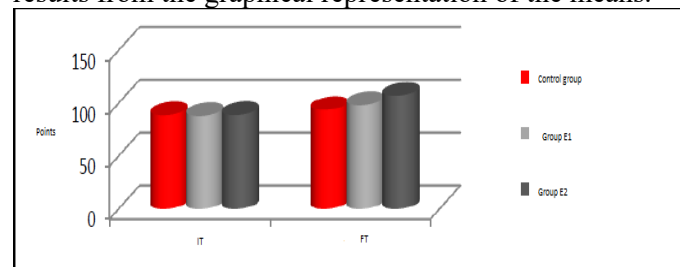


**Fig 1.** Graphical representation of athermic averages of effort capacity

**Fitness index (FI).** The calculation of the fitness index (FI), which represents the level of maximum oxygen absorption capacity in relation to age, sex, weight and height [5,12], shows that all research subjects showed increases in the arithmetic mean between tests, but those of the experiment groups were superior to the progress made by the control group.

The control group obtained a difference of the arithmetic means of 4.88, which determined a transition to a higher level, so in the initial test the subjects were at a score of 88.98, and in the final test they evolved at a score of 93.87.

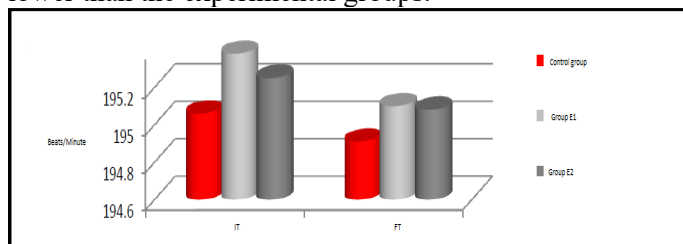
The results obtained in the final evaluation are on average higher than the initial evaluation, which determined a progress in the experimental groups of the fitness index (IF) level. The differences of the arithmetic means between group tests are: in the E1-Aquagym group of 10.02, and in the E2-Aquagym group of 17.98, as it also results from the graphical representation of the means.



**Fig 2.** Graphic representation of environments - Physical condition index

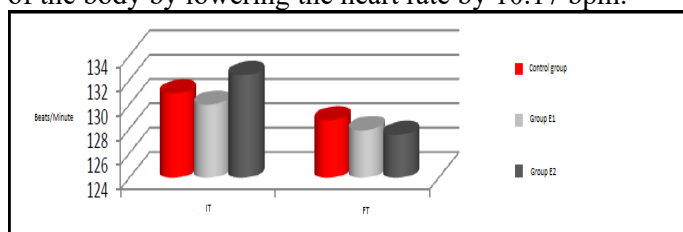
**Maximum heart rate HR max.** Following the research, by completing the 2 km gait test, the cardiac capacity represented by HR max., Decreased the arithmetic mean, in all subjects, in the final test compared to the initial test. The experimental group E1- aquagym, recorded a difference of the averages between the two tests of 0.28 b / min, and the experimental group E2- aquagym a decrease of the averages by 0.17 b / min., This parameter of the functional capacity is directly dependent on the age of the subjects during the experiment. The control group

obtained an initial value of 195.06 on the initial test and 194.91 on the final test, the difference being 0.15 b / min, lower than the experimental groups.



**Fig 3.** Graphical representation of HR max

Heart rate after exercise in the 2 km gait test. Heart rate after exertion at the 2 km walk test, in the final test compared to the initial test was better in all groups, especially in group E2 compared to the control group. After completing the 2 Km walking test, a significant progress of the FC indicator was observed after exertion, registering a difference of the arithmetic means between tests of 2.1 bpm in group E1-Aquagym, of 5.4 bpm in group E2 - Aquagym and of 2.2 bpm the control group. The statistical analysis with the t-Student test is insignificant, the values of p being higher than 0.05, which determines the acceptance of the null hypothesis at this functional cardiac indicator. The values recorded by us confirm the previous results of various studies. An important factor to consider is the environment, water, which under normal conditions determines an adaptation of the body by lowering the heart rate by 10.17 bpm.



**Fig 4.** Graphical representation of FC averages after effort in the 2 km walking test

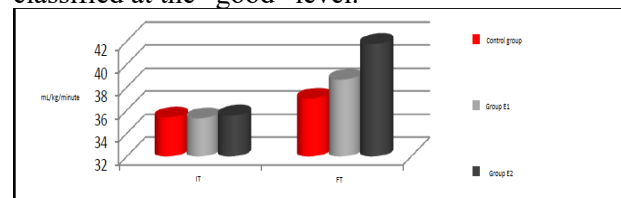
**Vital capacity. VO2max.** determined by performing the 2 km gait test recorded a higher average difference in both experimental groups compared to the control, following the application of operational programs specific to aquatic activities.

The control group obtained in the initial test an average value of 35.39 mL / Kg / min, and in the final test 37.02 mL / Kg / min, with an improvement difference of 1.63 mL / Kg / min. The E1-Aquagym experimental group recorded a progression of the mean difference of 3.36 mL / Kg / min. The most obvious improvement was found in the experimental group E2, the average difference between the tests being 6.21 mL / Kg / min.

Comparing the results of the experimental groups with the control group between tests: between the E1 group and the control group the average difference was 1.73 mL

/ Kg / min, and between the E2 group and the control group 4.58 mL / Kg / min.

Statistical analysis by the t-Student test shows a significant strong threshold, thus accepting the alternative hypothesis. According to the vital capacity assessment grid, at the initial testing all the samples were classified at the “average” level, and after the experiment they were classified at the “good” level.



**Fig 5.** Graphic representation of average VO2max

## Conclusions

The systematization of water activities on objective criteria effectively contributes to their knowledge, while allowing them to be included in the spectrum of recreational, sporting, relaxing or therapeutic activities. Introduction of a new activity, with a specific, innovative methodology called aqua gym, is part of the modern development and research trends of the activities domestically and internationally. Studying the development of motor skills through aquatic recreational activities, it is a modern trend, which in general can contribute to improvement human performance.

## Author contributions.

All the authors had the same contribution.

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## Rehabilitation Challenges in Limb-Girdle Muscular Dystrophies



WEB OF SCIENCE

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### Abstract

Limb-girdle muscular dystrophy (LGMD) is a burdensome progressive neuromuscular disease, with a great impact upon quality of life. Unlike other types of neuromuscular dystrophies, which have onset in early childhood and severely limit the life expectancy, LGMD is usually diagnosed at young adulthood age. Since no etiological treatment is currently available, physiotherapy and generally, rehabilitation therapy, are mandatory for preserving the functional capabilities of the muscles for as long as possible. Exercise therapy, electrical stimulation or novel therapies such as exoskeleton devices aim towards alleviating the impact of disability. It is ideal that muscular dystrophy should be assessed in interdisciplinary clinics (physical therapy, neurology, cardiology, pneumology, surgery and orthopedics) for proper long-term care.

**Keywords:** LGMD, muscle strength, rehabilitation, quality of life,

### Introduction

Limb-girdle muscular dystrophy (LGMD) is a group of genetic conditions that includes various phenotypes, with predilection to impairment of shoulder and pelvic girdles, as well as proximal muscle weakness. Different myopathic subtypes of the disease have a wide range of manifestations, which in some cases manifest in early childhood, and in other case, during adulthood [1, 2]. Degeneration of muscle fibers and the resulting loss of strength are determined by genetic mutations that determine different pathogenic mechanisms [3].

The underlying genetic conditions of LGMDs are either autosomal dominant (LGMD1) or autosomal recessive (LGMD2) [2]. These determine progressive degeneration of muscle fibers, loss in strength and difficulties of muscle fibers in maintaining physical structure during contraction [3].

More than 60% of the patients with muscle dystrophy experience important fatigue, a common sign of early disease, as physical activity and normal endurance produce discomfort [3]. The disease typically manifests during the second or third decade of life, with variable progression towards disability within the next 20-30 years. Tibial and peroneal innervated muscles are involved in the pathological process, usually with respect to facial muscles [4].

Although life expectancy is slightly reduced, the progressive motor disability and the respiratory or cardiac complications, have a huge impact upon quality of life, thus the need of proper rehabilitation programs and interdisciplinary approach.

### Clinical case

A 42 years old male patient is evaluated both clinically and by electromyography for follow up of a muscular dystrophy, limb-girdle type. An initial diagnosis suggestive for myopathy has been first established around the age of 17. According to the patient's medical history, the first manifestations occurred around the age of 14, with fatigue and discrete loss of muscle strength in proximal muscles, especially in the lower limbs. Until that moment, the patient had been an active child and teenager, and had been practicing different sports, including professional dancing. In spite of this diagnosis, especially due to the slow evolution of signs and symptoms, he continued to perform in a dance crew until nearly the age of 30. That was the moment when the patient looked for medical advice again, after almost 15 years, and the final diagnosis of LGMD has been established by clinically and electrophysiological methods. As the motor deficit in the lower limbs progressed by the age of 35, with difficulties in lifting the



legs, he started physical therapy. A muscle biopsy has never been performed, nor genetic tests, which were at the time, unavailable.

At the current visit, from clinical point of view, the patient had poor balance (he used a cane while walking), arms and shoulders held backwards with the abdomen prominently visible while walking and knees bent backwards. Getting up from seated position evoked the classic Gower's sign, usually seen in children and teenagers with Duchene or Becker dystrophies: the need of a dystrophic patient to use the hands and arms to "climb" up his own body from squatting position.

Some uncertain, undocumented, history of episodes with loss of conscience in early childhood might have made a difficult differential diagnosis at a certain time, as a mitochondrial myopathy should be taken into consideration knowing such facts. However, the clinical evolution, the clinical signs and electromyography (EMG) tests have been suggestive for LGMD during the years.

At the EMG study, both sensory and motor conduction studies for the median nerve, peroneal and tibial nerve were normal. Needle EMG was performed in the following muscles: right tibialis anterior, left vastus lateralis, left deltoid, left extensor digitorum communis and mentalis. Insertion of the needle electrode was difficult through the dense thickened muscle tissue, with no spontaneous activity, and with short duration and reduced amplitudes of the motor unit action potential (MUAP), with myopathic fast and reduced amplitude recruitment. This EMG aspect is suggestive for the discussed diagnosis.

As the disease progresses and the motor deficit worsens, the question that arises is: what is the best therapeutic approach to a patient with this diagnosis, for postponing a greater disability and maintaining a decent quality of life for as long as possible?

### **Aspects of rehabilitation in LGMD**

According to the model of inheritance, LGMDs can be either autosomal dominant (LGMD1) or autosomal recessive (LGMD 2). Different variants of cardiac and respiratory muscles affection, joints and muscles impairment, are considered patterns of the underlying genetic type [5].

Muscle strength and respiratory function are worthy parameters to monitor for assessing QoL, especially as loss of muscle strength limits the ability of walking and performing activities of daily living [6]. Results of respiratory muscle training in patients with LGMD in randomized control trials yet seems to be uncertain [7].

Either because of muscle fiber loss or because of the motor deficit related to a sedentary lifestyle, effort tolerance is affected in LGMD patients. There is debate whether physical exercise fights the loss of muscle fibers

and muscle strength or, on the other hand, it might induce damage within muscles due to the unstable sarcolemma, especially because of intense contractions during movement [3].

LGMD is related to the inability of muscle fibers of maintaining their physical structure during contraction, with damage of the sarcolemma, progressive degeneration of muscle fibers and loss of strength. Alteration of energy metabolism in the muscle fibers is also considered to be involved in the pathological background of the disease. These changes add to the loss of skeletal muscle mass, and manifest as muscle fatigue [3].

Muscle fatigue can be defined as the inability of continuing an intended physical activity, or as the excessive discomfort felt by the patient when trying to continue a physical effort. The underlying mechanisms also include the failure in calcium release from the sarcoplasmic reticulum, as well as the oxidative stress [3].

A normal physical training activity is composed of strength training (repeated muscle contraction against resistance) and aerobic exercise (the use of large muscle groups, continuously and rhythmical) [3]. Strength training and aerobic exercises in patients with LGMD, both at moderate intensity for long period of times are considered to be beneficial, not only for improving muscle, cardiac and respiratory function and preventing muscle atrophy, but also in prevention type 2 diabetes and other sedentary lifestyle related pathologies. This contrasts the fear of muscle overuse, although ischemia or hypoxia in the muscles can occur during prolonged exercises [3]. Muscle damage can result from altered mechanisms of the creatin kinase (CK), lactate dehydrogenase (LDH), myoglobin and troponin in case of intensive exercises. However, supervised aerobic exercise appears to be safe, if performed under supervision. It is also considered that physical exercise can be both safe and useful, no matter the type of training, as long as the intensity is low or moderate [3].

Strength training dedicated to specific muscles should be performed under professional supervision, especially as the optimal resistance needed is usually difficult to estimate, and because myalgia and CK increase should be avoided. Aerobic training can also improve muscle function, especially treadmill walking [5].

LGMD various disease subtypes have a profound impact upon the quality of life (QoL), especially as cardiopulmonary affection manifests as the illness progresses [1]. QoL tends to be seriously impaired by issues also concerning physical health (muscle weakness, limitation of motility and walking), mental health (emotional distress and impaired body image) and social limitations. Physical therapy in these patients can provide motivation and purpose [1].

Patients with LGMD should have the possibility to benefit from multiple specialties such as: physical therapy, occupational therapy, respiratory therapy, orthopedics and genetics [2]. As the disease progresses, some cases might even require surgery, especially scoliosis corrective surgery techniques such as spinal fusion, or tendon surgery [8].

High voltage pulsed galvanic stimulation (HVPGS), rather than other electrical stimulation methods, seems to positively influence muscle contraction, also providing benefits upon muscle strength and reducing pain [9]. HVPGS even turns out to be more effective than moderate physical therapy according in small studies, with need of further trials for confirmation [9].

The diagnosis is difficult to be perceived by the patients, as one is usually overwhelmed by concerns about the disease progression and how it will eventually imply coping with new ways of living. The transition from receiving the diagnosis towards the necessity of using a wheelchair should be supported by regular controls and psychological support. Part of this, the patient should be engaged in meaningful activities in society [10]. Using clinical scales initially designed for other types of muscular dystrophies might also be of help in LGMD, especially assessing performance of the upper limb [11]. Exoskeletons are already been used in rehabilitation in various neurologic disorders. Sczesny-Kaiser et al propose the hybrid assistive limb voluntary-driven exoskeleton for improvement of endurance of walking function, as part of a treadmill therapy program, with promising results [5].

Anti-gravity training combined strength (squats, calf rises and lunges) and aerobic exercises (walking or jogging in place), 3 times a week, according to Jensen et al, improves the closed-kinetic-chain leg muscle strength, but not the isometric knee extension strength or capacity of absolute explosion force production [12].

Even though involvement of the cardiovascular system can limit physical activity in patients with LGMD, and exercising in excess is to be avoided, it is important to encourage a healthy lifestyle and physical active life [13].

### Conclusions

Exercise is useful in LGMD for improving muscle strength, joint mobility and delaying progression towards disability, as much as possible. In absence of available disease modifying treatments, a rehabilitation strategy adapted to individual needs emerges as essential. Maintaining walking and overall active mobilization of the patient also has favorable effect on the quality of life.

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## Analgesic and anti-inflammatory activity of Artemisia extracts on animal models of nociception



WEB OF SCIENCE

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### Abstract

**Introduction.** The study aims to assess the antinociceptive and anti-inflammatory activity of extracts obtained from indigenous species of wormwood: *Artemisia absinthium*, *A. annua*, *A. vulgaris* and *A. pontica*.

**Materials and methods.** For these experiments, we employed nociception models using thermal stimulus (hot plate and tail immersion tests,  $t = 52.5^{\circ}\text{C}$ ; 30, 60 and 90 minutes testing), chemical stimulus (Zymosan-induced abdominal constriction response test, using distinct lots and testing at 60, 90 and 120 minutes after administration of samples) and pressure stimulus (Randall Selitto test) and an inflammation model for the evaluation of inflammatory edema by Plethysmometer test. Groups of 6 Swiss mice / lot were used, receiving by oral administration the plant extracts suspended in 0.1% CMC-Na. The doses were administered in geometric progression. Chemical analyses were performed by HPLC-MS in order to identify bioactive substances present in extracts: methoxylated flavonoids, sesquiterpene lactones, phytosterols and hydroxycinnamic acids.

**Results and discussion.** All plant extracts showed antinociceptive action on the models with thermal stimulus, as demonstrated by the  $\text{ED}_{50}$  values obtained at different test times. In the models of nociception with chemical and mechanical stimulus, models based on inflammatory mediation, the studied fractions have partially proved their antinociceptive action. Regarding the degree of inhibition of inflammatory edema, the highest potency was exhibited by *Artemisia pontica* extract (86.5% inhibition for the dose of 100 mg/kg). Hispidulin and eupatorin, known anti-inflammatory compounds, were identified in all extracts, along with caffeic and chlorogenic acids, stigmasterol, campesterol and  $\beta$ -sitosterol.

**Conclusions.** The obtained results support the use of these plant extracts in moderate intensity pain, triggered by both central and peripheral mechanisms.

**Keywords:** hot-plate test, tail immersion test, abdominal constrictive response, Randall-Selitto test, inflammatory edema,

### Introduction

The *Artemisia* genus - wormwood, includes over 500 species, widespread around the globe, especially in the northern hemisphere. These are aromatic, medicinal and food plants, many being used in the folk medicine of different countries in various diseases (1). The Romanian Pharmacopoeia includes the monograph *Absinthii herba* (the aerial parts of *Artemisia absinthium*) with the indication bitter tonic, but it is also recommended as cholagogue and anthelmintic (2). Similarly, *Artemisia pontica* is used as tonic and anthelmintic, sometimes as a substitute for *A. absinthium*, although its properties are milder than those of common wormwood (3). *Artemisia vulgaris* is a cosmopolite species, known as tonic, hypoglycemic, emmenagogue, anti-septic, analgesic, and anti-helminthic, frequently utilized in Chinese medicine in combination with acupuncture treatment (4).

Research on *Artemisia* species intensified with the discovery of artemisinin, an antimalarial compound from

*Artemisia annua*, which also exhibits antiphlogistic, immunomodulatory, anticancer and antimicrobial effects (5). The analgesic and anti-inflammatory actions of *Artemisia annua* extracts are attributable to the sesquiterpene lactones, such as artemisinin, but also to flavonoids, phenolic acids and coumarins (6, 7).

In the present study we aimed to evaluate the antinociceptive and anti-inflammatory action of crude methanol extracts obtained from wormwood species widespread in the Romanian flora: *A. absinthium* - wormwood, *A. vulgaris* - common mugwort, *A. annua* - sweet wormwood and *A. pontica* - Roman wormwood. The plant extracts were then chemically characterized by liquid chromatography-mass spectrometry analysis in order to identify biologically active compounds, such as sesquiterpene lactones, methoxylated flavones, phytosterols and polyphenols.

## Materials and methods

### Plant material and extraction procedure

The aerial parts of *Artemisia annua* L., *A. vulgaris* L., *A. absinthium* L. and *A. pontica* L. were harvested at the flowering stage (July-September) from the countryside around Iasi, Romania. The species were identified by a specialist and voucher specimens were deposited in the Herbarium of Pharmaceutical Botany Department from "Grigore T. Popa" University of Medicine and Pharmacy. The plants were air-dried at room temperature and grounded to a fine powder. The extracts were obtained by maceration of dry plant material (300 g) with methanol (1:10 ratio m/v) for 24 hours with continuous agitation. Extract solutions were filtered and evaporated to dryness to afford the crude methanol extracts, labeled A<sub>1</sub> - *A. annua* (41,23 g), A<sub>2</sub> - *A. vulgaris* (25,64 g), A<sub>3</sub> - *A. absinthium* (34,63 g) and A<sub>4</sub> - *A. pontica* (43,85g). The extracts were appropriately diluted before injection in HPLC.

### Pharmacological study

**Animals.** In this study we used male Swiss mice provided by the "Cantacuzino" Institute Bucharest, Romania, weighing 20-30 g. All animals were housed at 21 ± 2°C under a 12-h light/dark cycle with access to standard food and water *ad libitum*. Prior to each experiment, animals were habituated to the testing room and the equipment for five consecutive days. Animals received orally, dose sequences in geometric progression (ratio 2) of the studied extracts. The extracts were suspended in 0.1% sodium carboxy-methylcellulose (CMC-Na) (Sigma), while the control group received only the vehicle, CMC-Na. Habitation conditions were set inside the laboratory of experimental pharmacodynamics in the department of Pharmacodynamics and Clinical Pharmacy, at "Grigore T. Popa" University.

**Ethics statement.** All experiments were conducted in strict conformity with the specific regulations approved by "Grigore T. Popa" University of Medicine and Pharmacy Iasi, European bioethical regulations (Directive 2010/63/EU) and International Association for the Study of Pain regulations.

**The hot plate test** was performed according to the method described by Woolfe and MacDonald with some minor modifications (8). The mice were individually placed in the cylindrical chamber of the hot plate (Model 7280 UGO Basile) on the heated surface at 52.5°C ± 0.1°C. The pain latency period was measured, with a 30 seconds cut-off. The response for testing the pain threshold at the thermal stimulus consists in licking and/or shaking the hind paw or the tendency to jump in order to leave the enclosure. The animals were tested for the thermal stimulus 1 hour before being treated, eliminating from the experiment the animals that did not respond in 15 seconds. After treatment, retesting was performed at 30, 60, 90 minutes, and the latency period of the pain

reaction was measured. Percentage inhibition of the response to the nociceptive stimulus was expressed according to the formula:

% inhibition =  $(T_x - T_0)/(T_m - T_0) \times 100$ , where T<sub>0</sub> - latency of the response measured prior to administration of the extract, T<sub>x</sub> - latency at different time intervals following administration of the test extract, T<sub>m</sub> - cut-off time.

**The tail immersion test** measures the latency period of the mouse pain reaction when the tail is fully immersed in hot water at 52.5 ± 0.1 °C for 15 seconds (cut-off). The time elapsed between immersion and purposeful withdrawal of the tail from the bath is recorded. Animals were tested for thermal stimulation 45 minutes before treatment, and animals that did not respond within 15 seconds were removed from the experiment. The experimental model was evaluated quantitatively as a quantal type. By successive determinations, the graded effect was transformed into a quantal one, by setting the 7-second threshold for non-responsive animals when applying the stimulus after treatment.

**Zymosan A-induced writhing test.** The principle of the method relies on the fact that through the intraperitoneal injection of a suspension of Zymosan A, a characteristic response is induced, represented by the stretching followed by the torsion of the body, abdominal retraction and opisthotonus. The test allows for the evaluation of the central and peripheral analgesia, and by using Zymosan, the test is more relevant for the pathogenesis of inflammatory pain. The test consists of the intraperitoneal administration of a suspension of Zymosan A, 40 mg/kg body weight and the recording of the abdominal constrictive responses for 12 minutes after that. The evaluation of the response was of the quantal type, characterized by the presence or the absence of the constrictive response. It was considered as antinociceptive effect of the extracts taken into study, the inhibition percentage obtained through the absence of the response of the total number of animals tested: % inhibition = (number of non-responders / total number of animals) x 100 (9).

**The Randall-Selitto assay** (10) allows the assessment of pain in inflammatory conditions. The test consists in applying a mechanical stimulus (Ugo Basile Analgesimeter 37215) on the inflamed paw of the animal (cut-off pressure 250 g). The edema is obtained by the subcutaneous injection into the plantar region of 3% saline suspension of lambda-carrageenan (Sigma) in mice. The stimulus is applied up to the cut-off value. The increase of the latency time of the pain reaction is recorded after 4 hours from the development of edema. The evaluation is made in comparison with the contralateral paw where only simple saline was injected (Zentiva). The antinociceptive effect was calculated according to the formula: % inhibition =  $(g_x + g_0)/(g_m -$



$g_0$ ) x 100, where:  $g_0$  – measured response latency before the administration of the tested extract,  $g_x$  - latency at different times following the administration of the extract,  $g_m$  - the maximum permissible weight (cut-off).

*Carrageenan-induced paw edema* is an experimental model of acute inflammation that allows the evaluation of the degree of inhibition of inflammatory edema induced by chemical stimulus. The test is performed by measuring the volume of the inflamed paw by subcutaneous administration in the plantar region of a 3% saline suspension of  $\lambda$ -carrageenan. The 7140 Ugo Basile plethysmometer was used to measure the volume of the inflamed paw 4 hours after the development of inflammatory edema compared to the contralateral paw of the treated groups compared to the control group. The assessment of the degree of inflammation has indicative value in the present study and was performed in parallel with the Randall-Selitto test for the sequence of doses that showed antinociceptive action. The results were expressed as percentage relative to the maximum possible effect level (MPE%) for each extract, using the formula: % inhibition = (M-T) / M x 100, where M - the value of the degree of inhibition of the control group and T - the value of the degree of inhibition of the treated group.

#### Chemical analysis of plant extracts

*The analysis of sesquiterpene lactones* was carried out by high-performance liquid chromatography coupled with mass spectrometry (LC-MS), using six standards: vulgarin,  $\alpha$ -santonin, dehidroleucodine, artemisinin, costunolide and alantolactone (Sigma, Germany). Calibration curves in the range 0.02 - 3  $\mu$ g/mL showed a linear correlation coefficient ( $R^2 > 0.99$ ) and were employed to quantify the lactones in the extracts (11).

*Methoxylated flavonoids* were identified through a LC-MS method described before (12). Six standards were used: jaceosidin, eupatilin (ALB Technology, China), casticin, acacetin, eupatorin, hispidulin (Sigma, Germany). Calibration curves in the 0.02 - 6  $\mu$ g/mL range with good linearity ( $R^2 > 0.99$ ) were used to determine the concentration of methoxylated flavones.

*Caffeic and chlorogenic acids* were determined quantitatively by a LC-MS method using standards acquired from Sigma, Germany. Calibration curves in the range of selected concentrations (0.06 - 4  $\mu$ g/mL) had a good linear correlation coefficient ( $R^2 > 0.99$ ) and were used to calculate the concentrations of the hydroxycinnamic acids (11).

*Phytosterols analysis* was performed by a previously reported LC-MS method (12) using five standards:  $\beta$ -sitosterol, stigmasterol, campesterol, brassicasterol and ergosterol, acquired from Sigma, Germany. Calibration curves of the sterols in the range of selected concentrations (0.06 - 6  $\mu$ g/mL) displayed a good linearity ( $R^2 > 0.99$ ).

## Results and discussions

### Pharmacological study

*The hot plate test.* A<sub>1</sub> extract was tested at doses of 25-200 mg / kg body weight p.o. in CMC-Na 0.1% and an MPE of 90.00% was obtained at 90 minutes. Extracts A<sub>2</sub>, A<sub>3</sub>, A<sub>4</sub> were tested at doses of 100-400 mg / kg body weight p.o. in CMC-Na 0.1%, obtaining the following values: MPE at 30 minutes (61.7%) for A<sub>2</sub> extract, MPE at 60 minutes (64.6%) for A<sub>3</sub> extract, and MPE at 30 minutes (62.6%) for the A<sub>4</sub> extract. By the administration of the mentioned dose sequences, in geometric progression, ratio 2, we could establish the median effective dose (ED<sub>50</sub>) value of each extract (Table 1).

**Table 1.** ED<sub>50</sub> values of extracts in the hot-plate test

ED <sub>50</sub> mg/kg body weight/p.o.			
A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>	A <sub>4</sub>
58.44 ± 4.784	263.62 ± 18.268	172.37 ± 33.762	202.10 ± 3.72
Y = - 87.238 + 77.680*X	Y = - 124.92 + 72.253*X	Y = -56.24 + 47.50*X	Y = - 51.863 + 44.182*X
R = 0.970	R = 0.994	R = 0.948	R = 0.998

*The tail immersion test.* A<sub>1</sub> extract at doses of 25-200 mg / kg body weight p.o. shows maximum possible effect at 90 minutes (83.33%). A<sub>2</sub> extract, tested at doses of 50-400 mg / kg body weight p.o. shows maximum possible effect at 60 minutes (100.00%). A<sub>3</sub> extract at doses of 100-400 mg / kg body weight p.o. exerts maximum possible effect at 90 minutes (83.33%). A<sub>4</sub> extract was tested at 50-400 mg / kg body weight and manifested maximum possible effect at 90 minutes (66.67%). The ED<sub>50</sub> values of tested extracts are shown in Table 2.

**Table 2.** ED<sub>50</sub> values of plant extracts in the tail immersion test

ED <sub>50</sub> mg/kg body weight/p.o.			
A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>	A <sub>4</sub>
59.41 ± 22.608	78.939 ± 27.469	236.55 ± 76,930	230.80 ± 94.29
Y = 2.044 + 1.666*X	Y = 0.845 + 2.190*X	Y = 0.416 + 2.281*X	Y = 0.858 + 1,753*X
R = 0.942	R = 0.891	R = 0.973	R = 0.950

*Zymosan A-induced writhing test.* The animals were treated orally with suspensions from dried plant extracts, in the doses sequence of 25-400 mg / kg body weight for A<sub>1</sub> and A<sub>2</sub>, 50-200 mg / kg body weight for A<sub>3</sub> and 100-800 mg / kg body weight for A<sub>4</sub>. The maximum possible effects of extracts were: 66.67% for A<sub>1</sub>, 50% for A<sub>2</sub>, 83.33% for A<sub>3</sub> and 66.66% for A<sub>4</sub> extract. The ED<sub>50</sub> values of tested extracts were calculated and presented in Table 3.

**Table 3.** ED<sub>50</sub> values of extracts in the writhing test

ED <sub>50</sub> mg/kg body weight/p.o.			
A <sub>1</sub>	A <sub>2</sub>	A <sub>3</sub>	A <sub>4</sub>
101.44 ± 44.40	177.72 ± 79.14	72.49 ± 24.79	346.64 ± 162.81
Y = 1,935 + 1,528*X	Y = 0.198 + 2.134*X	Y = 0.624 + 2.352*X	Y = 1.607 + 1.336*X
R = 0.998	R = 0.953	R = 0.990	R = 0.906

*The Randall-Selitto test.* A<sub>1</sub>-A<sub>4</sub> extracts were analyzed at doses of 100-400 mg / kg body weight p.o. in 0.1% CMC-Na. A<sub>1</sub>-A<sub>3</sub> extracts showed a hyperalgesia tendency for the studied dose sequence. A<sub>4</sub> extract showed a maximum possible effect of 49% at a dose of 100 mg. The value obtained could allow the study to be continued for another doses sequence.

*Inflammatory edema test.* A<sub>1</sub>-A<sub>4</sub> extracts were tested at doses of 100-400 mg / kg body weight p.o. in 0.1% CMC-Na. Regarding the degree of inhibition of inflammatory edema, the following data were obtained: A<sub>1</sub> extract shows MPE = 50% at a dose of 400 mg / kg body weight, A<sub>2</sub> extract exerts MPE = 56.3% at a dose of 200 mg / kg body weight, A<sub>3</sub> extract manifest MPE = 49% at a dose of 100 mg / kg body weight and A<sub>4</sub> extract presents MPE = 86.5% at a dose of 100 mg / kg body weight. These values support the validity of the working hypothesis, which encourages further study.

#### Chemical analysis of plant extracts

Phytochemical analyzes identified in all plant extracts variable concentrations of caffeic and chlorogenic acid, these compounds being predominant in the A<sub>2</sub> extract (Table 4). The anti-inflammatory activity of chlorogenic acids, esters formed between quinic acid and trans-cinnamic acids, is well documented and traceable to their ability to relieve intracellular oxidative stress and to inhibit pro-inflammatory cytokines by regulation of key transcription factors (13).

**Table 4.** Concentration of the hydroxycinnamic acids in the tested extracts (µg/g dry extract)

	Caffeic acid	Chlorogenic acid
A <sub>1</sub>	211.66	11786.66
A <sub>2</sub>	235.71	19112.5
A <sub>3</sub>	126.66	9750
A <sub>4</sub>	203.12	14718.75

LC-MS analysis of phytosterols revealed in all extracts the presence of stigmasterol, sitosterol and campesterol (Table 5). Sitosterol predominates in all four extracts, while ergosterol is found only in small amounts in samples A<sub>2</sub> and A<sub>3</sub>. Besides their cholesterol-lowering effect, plant sterols have been shown to reduce plasma levels of C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), phospholipase A1, and

fibrinogen, thus manifesting anti-inflammatory activity (14).

**Table 5.** Concentration of phytosterols in the tested extracts (µg/g dry extract)

	ergo-sterol	stigma-sterol	β-sito-sterol	campe-sterol	brassica-sterol
A <sub>1</sub>	-	1981.66	5367.83	192.5	-
A <sub>2</sub>	25.53	1406.96	9841.78	147.32	15.53
A <sub>3</sub>	3.16	666.16	3545.16	67.83	-
A <sub>4</sub>	-	448.59	7581.71	52.96	-

In the A<sub>3</sub> extract, the sesquiterpene lactones costunolide and dehydroleucodine were identified. They are cited in the literature for their antinociceptive and anti-inflammatory action (15, 16).

As expected from a previous study (17), the A<sub>1</sub> extract contains high amounts of artemisinin. Analgesic and anti-inflammatory activity of artemisinin is well documented in the specialty literature (18, 19). Numerous studies have shown that artemisinin is able to decrease neutrophils count, suppress the secretion of cytokines, inhibit macrophage activation and their responses, and block lymphocytes proliferation. The anti-inflammatory effects of artemisinin is owed to the inhibition of different signaling pathways (19). Additional research demonstrated that artemisinin modulates neuropathic pain and its antinociceptive activity is mediated by γ-aminobutyric acid A (GABA<sub>A</sub>) receptors (18).

Costunolide, was also identified in A<sub>1</sub> and A<sub>2</sub> extracts. Costunolide modulates various intracellular signaling pathways involved in tissue inflammation, including intracellular kinases and redox-regulated transcription factors, and also reduces the production and expression of pro-inflammatory mediators, such as cyclooxygenase-2, inducible nitric oxide synthase, nitric oxide, prostaglandins, and cytokines (15).

Allantolactone, vulgarin and santolin were not identified in the tested extracts and none of the standards lactones used were found in the A<sub>4</sub> extract, as seen in Table 6.

**Table 6.** Concentration of sesquiterpene lactones in the tested extracts (µg/g dry extract)

	artemisinin	costunolide	dehydroleucodine
A <sub>1</sub>	6790.35	361.28	-
A <sub>2</sub>	-	866.79	-
A <sub>3</sub>	-	10.71	454.7

Among the methoxylated flavones with anti-inflammatory action (20-22), specific to the genus *Artemisia*, hispidulin and eupatorin were found in all extracts, while jaceosidine was not identified in the analyzed samples. Casticin was found in extracts A<sub>1</sub>-A<sub>3</sub>, notably in A<sub>1</sub> extract. Eupatilin was identified in small

quantities only in A<sub>1</sub> extract, while acacetin only in A<sub>4</sub> extract.

Flavonoids usually manifest antiphlogistic activity by modulating pro-inflammatory gene expression and intervening in multiple signaling pathways, chiefly nuclear factor – kappa B (NF-κB) and mitogen-activated protein kinase (MAPK). The anti-inflammatory response of flavonoids seems to be signal specific and dependent on the cell type. In addition, flavonoids have the ability to scavenge free radicals and manifest antioxidant activity, thus reducing intracellular oxidative stress and inflammation. However, they can act as a pro-oxidant at high concentrations and caution is necessary when administering flavonoids (23).

**Table 7.** Concentration of methoxylated flavonoids in the tested extracts (µg/g dry extract)

	eupatorin	eupa-tilin	aca-cetin	casticin	hispidulin
A <sub>1</sub>	67.30	7.86	-	5237.14	102.79
A <sub>2</sub>	6.58	-	-	446.65	14.69
A <sub>3</sub>	121.73	-	-	688.33	32.71
A <sub>4</sub>	4.47	-	41.53	-	368.85

It seems that high amounts of sesquiterpene lactones and methoxylated flavonoids, as found in A<sub>1</sub> extract, could be correlated with potent analgesic effects manifested in the thermal stimulus model of nociception.

## Conclusions

The present study carried out the evaluation of the antinociceptive activity of some *Artemisia* species from the spontaneous flora of Romania. In addition to pharmacological testing, the chemical characterization of the extracts in terms of biologically active compounds was performed. On the pharmacological models with thermal stimulus, the studied extracts demonstrated antinociceptive action through the ED<sub>50</sub> values obtained, with *A. annua* extract being the most efficient. On the nociception models with chemical and mechanical stimulus, models based on inflammatory mediation, the studied fractions partially proved their antinociceptive action. *A. pontica* extract exhibited good anti-inflammatory activity against carrageenan induced paw edema. The results obtained support the use of these extracts in pain of moderate intensity, triggered by both central and peripheral mechanism. Further studies are needed to isolate the bioactive fractions and compounds and to evaluate their antinociceptive and anti-inflammatory actions.

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## *In vivo* antinociceptive and anti-inflammatory potential of hesperidin and its cyclodextrin inclusion compounds



WEB OF SCIENCE

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### Abstract

**Introduction.** This study aims to evaluate the antinociceptive activity on inflammatory and non-inflammatory nociception models, as well as the anti-inflammatory action of hesperidin and its inclusion compounds with beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin. **Material and method.** For these experiments, we employed nociception models using thermal, chemical and pressure stimuli and an inflammation model for the evaluation of inflammatory edema by plethysmometer test. **Results and discussions.** The obtained results demonstrate that the HES- $\beta$ CD inclusion compounds exhibited antinociceptive action predominantly on experimental non-inflammatory nociception models, while HES-HP- $\beta$ CD exhibited anti-inflammatory and antinociceptive activities predominantly in inflammatory nociception models. **Conclusions.** This research may be the starting point for future studies regarding the improvement of biopharmaceutical qualities of HES by encapsulation in cyclodextrins.

**Keywords:** *hesperidin, cyclodextrin inclusion compounds, antinociceptive, anti-inflammatory activity,*

### Introduction

Research regarding reduction of side effects and optimization of medications have led to the development of new compounds with improved therapeutic potential. One of the problems encountered in the formulation of oral drugs is substance solubility, the dissolution capacity and dissolution rate greatly influencing the absorption process through the gastrointestinal mucosa. The solubility of certain substances can be improved using one of the most modern methods, complexation, which consists in inducing a reversible association between a substrate and a ligand to form new chemical species.

Cyclodextrins (CDs) are obtained through the enzymatic degradation of starch and have the shape of a truncated cone with a lipophilic cavity and a hydrophilic outer surface. Consequently, CDs can form inclusion compounds in which the “guest” molecule is partially or completely included in the “host” molecule, the most important conditions being steric and thermodynamic factors (1, 2).

First generation CDs are natural and contain 6-8 units of glucopyranose, having a limited solubility in water, such as  $\beta$ -cyclodextrin ( $\beta$ -CD) with a solubility in water of 18.5 mg/L. Therefore, chemical or enzymatic modifications of CDs have been used. One such example consists of substituting hydrogen and hydroxyl groups with various substituents, such as alkyl, hydroxyalkyl, carboxyalkyl, glucosyl, that lead to the formation of CDs

with increased solubility, such as hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD), that has a water solubility of more than 600 mg/mL (3).

CDs have a wide range of applications in the pharmaceutical industry, such as increasing the solubility, stability and dissolution rates of active substances, reducing the unpleasant taste and smell of substances, preventing interactions between active substances or between active substance and excipients, as well as controlled release of the active substance (4).

Flavonoids were the subject of a great number of researches in the plant physiology field, being involved in complex biological processes in the cell and cell membrane. Worldwide, statistics show a large number of papers that record data about their structure, synthesis and pharmacodynamic actions. Since flavonoids represent the majority of plant polyphenols, they were relatively rapidly isolated, being major candidates in research. For the current study, hesperidin was chosen from this class of compounds for inclusion in cyclodextrins.

Hesperidin (HES) is a flavanone glycoside, which is sparingly soluble in water and therefore has a limited bioavailability. However, it possesses important pharmacological actions such as: antioxidant, antitumoral (5), improving capillary status by permeability reduction and capillary resistance enhancement (6), lowering

cholesterol, lipid levels and blood pressure, diuretic effect and anti-replicative activity against some viruses (7).

Moreover, it has anti-inflammatory and analgesic effects through the inhibition of eicosanoid synthesis or of histamine release (8). It has also been shown that HES can be an effective therapeutic agent in improving the chondrogenesis of human mesenchymal stem cells by inhibiting inflammation and thus facilitating connective tissue repair (9).

In the last years, HES has also been shown to have important neuroprotective properties in neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases (7).

The motivation of our study was driven by the therapeutic importance and the physicochemical properties of HES, one main objective of the current research being the improvement of its biopharmaceutical qualities by encapsulation in cyclodextrins. Therefore, our research has included the preparation of inclusion compounds with  $\beta$ -CD and HP- $\beta$ -CD by different methods. The inclusion in CDs was demonstrated by various methods such as: solubility studies, UV-Vis spectroscopy, TLC, NMR, FTIR, thermal methods. Afterwards, the *in vitro* dissolution kinetics of inclusion compounds compared to free HES was studied. The results confirmed an increase in the dissolution of inclusion compounds in simulated gastric fluid at a pH of 1.2. Further *in vitro* studies have focused on assessing the antimicrobial and antioxidant activities of the inclusion compounds compared to free HES. The tests demonstrated an increase of these properties for inclusion compounds (10-12).

To the best of our knowledge, this is the first study that aims to evaluate the antinociceptive activity of these inclusion compounds (HES- $\beta$ CD and HES-HP- $\beta$ CD) on inflammatory and non-inflammatory nociception models, as well as their anti-inflammatory action compared to free HES.

## Materials and methods

**Samples:** HES and its inclusion compounds with  $\beta$ -CD and HP- $\beta$ -CD were administered in 1 % CMC-Na suspension p.o. All tests included a sequence of dose values in geometrical progression, in the range of 100-400 mg/kg HES and amounts of inclusion compounds with an equivalent HES content.

**Chemicals:** sodium carboxymethyl cellulose (CMC-Na) (Sigma); Zymosan A (Sigma) and  $\lambda$ -carrageenan (Sigma) suspended in physiological saline solution (Zentiva).

**Animals:** The study was carried out on adult male Swiss albino mice, weighing 20-25 g, that were purchased from the Cantacuzino Institute (Bucharest) and transported according to the current legislation. The proper housing conditions were established by the Experimental Pharmacodynamics Laboratory, Department of Pharmacodynamics and Clinical Pharmacy, Faculty of

Pharmacy, "Grigore T. Popa" University of Medicine and Pharmacy Iasi. These conditions consisted of: laboratory enclosure under constant and controlled temperature ( $21 \pm 2$  °C) and humidity, and a 12 hours light-dark cycle (7.00 am - 7.00 pm); Mini Duna plexiglas cages provided with water and food bowls, which allowed feeding with standard diet (Biobase Baneasa) and water *ad libitum*.

Since the tests examine the behavioral reactions of animals, a period of 10 days for acclimatization was established prior to the beginning of experiments, in which observations regarding their behavior in terms of water and food consumption, neurological signs, etc., were made. The animals were randomly allocated to treatment groups of 6-10 mice/group and 3 hours before each test, the access to food and water was stopped.

All experiments were conducted in accordance with the specific regulations approved by "Grigore T. Popa" University of Medicine and Pharmacy Iași, European bioethical regulations (13) and International Association for the Study of Pain (IASP) guidelines.

**Apparatus:** thermostatic system Hot Plate Ugo Basile 7280 model, Ugo Basile Analgesimeter 37215 model, Ugo Basile plethysmometer 7200 model.

**Methods:** In order to evaluate the antinociceptive action of HES and its inclusion compounds the following tests on inflammatory and non-inflammatory nociceptive models were used: by thermal stimulus: the hot plate test and the tail immersion test; by chemical stimulus: the constrictive abdominal response test; by mechanical stimulus: Randall-Selitto test. The anti-inflammatory action was evaluated using the inflammatory edema test.

### The hot plate test

This test was carried out according to the method established by Woolfe and Mac Donald 1994 and modified by Eddy and Leimbach 1953; O'Callaghan and Holzman, 1975 (14). The animals were subjected to a preliminary test, after which the samples were administered. Each mouse was placed into a closed cylindrical space with a metal hot plate maintained at a constant temperature of  $52.5 \pm 0.1$  °C, for 30 seconds (cut-off time). Pain response latency was determined at 30, 60, and 90 minutes after sample administration. This experiment produces two types of behaviors (paw-licking and jumping), for which reaction times can be measured (14-18). The evaluation was based on a graded response and the antinociceptive effect was calculated using the following formula:

$\% \text{ Inhibition} = (T_x - T_0) / (T_m - T_0) \times 100$	<b>(1)</b>
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where:

$T_0$  – response latency measured before sample administration

$T_x$  – response latency measured after sample administration, at different periods of times

$T_m$  – cut-off time, set in order to avoid injury in animals.

### Tail immersion test

In this case, the method of Ben-Bassat et al., 1959 and Janssen et al., 1963, modified by Grotto and Sulman, 1967 (14) and Bild et al. 2009 was used (19). The experiment was conducted by immersing the animal's tail in a thermostated water bath at  $52.5 \pm 0.1$  °C for 15 seconds (cut-off time), at 30, 60 and 90 minutes after sample administration (14, 17, 19). Pain reaction time was monitored by tail retraction. The evaluation was based on a quantal response and the antinociceptive effect was calculated using the following formula:

$$\% \text{ Inhibition} = (\text{no. non-responders} / \text{total no. of animals/group}) \times 100 \quad (2)$$

### The constrictive abdominal response test

The method of Siegmund et al., 1957, Koster et al., 1959, modified by Domer, 1971; Tallarida et al., 2003; Turner and Hebborn, 1965 (16) and Bild et al. 2017 was applied (20). 60, 90 and 120 minutes after the administration of test samples, the groups received a Zymosan A saline suspension 20 mg/kg i.p. (intra-peritoneally). When administered i.p., Zymosan A has the capacity to produce a characteristic response called abdominal constriction response, characterized by elongation and constriction of the animal, abdominal retraction and opisthotonos. The number of abdominal constriction responses was recorded for 12 minutes after administration of Zymosan A (17, 20).

The evaluation was based on a quantal response and the antinociceptive effect was calculated using the following formula:

$$\% \text{ Inhibition} = (\text{no. non-responders} / \text{total no. of animals/group}) \times 100 \quad (3)$$

### The Randall-Selitto test and inflammatory edema test

The experiment was performed according to a method modified by Bild et al. 2011 (21). After administration of test samples, an irritant agent capable of producing edema ( $\lambda$ -carrageenan, 3 % saline suspension) was injected s.c. (subcutaneously) into the plantar region. A mechanical stimulus (a cut-off pressure of 250 g) was applied on the inflamed paw, followed by the measuring of its withdrawal latency, 4 hours after administration of the inflammatory agent (14, 17, 21, 22). The evaluation was based on a graded response and was made by comparison with the contralateral paw, in which only saline solution was injected. The antinociceptive effect was calculated using the following formula:

$$\% \text{ Inhibition} = (g_x - g_0) / (g_m - g_0) \times 100 \quad (4)$$

where:

$g_x$  – response latency measured after sample administration

$g_0$  – response latency measured before sample administration

$g_m$  – cut-off time.

Further testing was done in order to assess the anti-inflammatory action by evaluating the capacity of samples to inhibit  $\lambda$ -carrageenan-induced edema. This test was completed by measuring the volume of the paw using the plethysometric method, 4 hours after administration of the inflammatory agent. The degree of the inflammatory edema inhibition was calculated according to the following formula:

$$\% \text{ Inhibition} = (M - T) / M \times 100 \quad (5)$$

where:

M – value of the degree of inhibition of the control group

T – value of the degree of inhibition of the treatment group.

### Results and discussion

The *in vivo* experiments performed in this study aimed to test the antinociceptive and anti-inflammatory actions of HES inclusion compounds with  $\beta$ -CD and HP- $\beta$ -CD, as well as of free HES. Consequently, the response to various thermal, mechanical, chemical nociceptive and inflammatory stimuli was tested.

After oral administration of samples (HES- $\beta$ -CD, HES-HP- $\beta$ -CD, free HES,  $\beta$ -CD and HP- $\beta$ -CD), the ED<sub>50</sub> values (mg/kg) were determined. The results are presented in Tables 1-4.

For  $\beta$ -CD and HP- $\beta$ -CD, the 50 % activity level could not be demonstrated for the studied doses in any of the performed tests.

### The hot plate test

The behaviors noticed during this test, that implies a thermo-algesic mechanism, are considered to be supraspinally integrated responses, which allow the evaluation of a compound as an opioid or non-opioid analgesic, considering the experimental conditions and the animal's type of reaction (14).

**Table 1.** ED<sub>50</sub> values (mg/kg body weight/p.o) for samples analyzed by hot plate test

Time	HES	HES- $\beta$ CD	HES-HP- $\beta$ CD
30 minutes	*	*	*
60 minutes	225.46 $\pm$ 15.34 TLC 168.36-853.05	165.89 $\pm$ 12.98 TLC 138.36-720.10	*
90 minutes	192.22 $\pm$ 23.11 TLC 110.25-890.25	*	*

\* level of activity < 50 %,

TLC - True Confidence Limits

According to the data presented in Table 1, the ED<sub>50</sub> values for free HES showed comparable antinociceptive action at 60 and 90 minutes. Among the inclusion compounds, for that with HP- $\beta$ -CD, the 50 % activity

level could not be achieved. However, HES- $\beta$ -CD inclusion compounds showed 50 % antinociceptive action at 60 minutes and showed superior potency compared to free HES.

#### **Tail immersion test**

This test completes the hot plate test for confirmation of the involvement of spinal structures for pain perception and integration, both measuring animal nociceptive response latencies to thermal stimuli (23).

**Table 2.** ED<sub>50</sub> values (mg/kg body weight/p.o) for samples analyzed by tail immersion test

Time	HES	HES- $\beta$ CD	HES-HP- $\beta$ CD
<b>30 minutes</b>	*	90.35 $\pm$ 32.52 TLC 20.29 – 198.6	*
<b>60 minutes</b>	240.21 $\pm$ 66.12 TLC 138.36-853.05	91.85 $\pm$ 28.63 TLC 17.29 – 176.4	*
<b>90 minutes</b>	203.58 $\pm$ 44.83 TLC 123.65-398.53	122.90 $\pm$ 36.67 TLC 30.61 – 312.13	*

\* level of activity < 50 %,

TLC - True Confidence Limits

For free HES, the antinociceptive action was over 50 % after 60 minutes and was maintained at 90 minutes. Administration of free HES and its inclusion compounds containing an equivalent amount of HES lead to similar results as those obtained in the previous test, regarding the difference between the two types of studied CDs (Table 2). For HES- $\beta$ -CD, the action was assessed for all studied temperature ranges, while HES-HP- $\beta$ -CD compounds didn't modify the reactivity of animals to painful thermal stimulation in a percentage that allows to obtain a level of activity over 50 %. The ED<sub>50</sub> values for the HES- $\beta$ -CD inclusion compounds were lower compared to the values obtained for the group treated with free HES, which demonstrates their superior potency.

Thermal nociceptive models are sensitive to opioid drugs and the analgesic activity is mediated by  $\mu$ ,  $\kappa$  and  $\delta$  receptors, which are located only in the central nervous system, but not by receptors located in the peripheral nervous system (23).

HES is a lipophilic substance, that has shown central analgesic and anxiolytic-sedative effects, suggesting that it may cross the blood-brain barrier (24). Loscalzo et al. demonstrated that the effects of HES are completely blocked by naltrexone, which is a non-selective opioid

antagonist, and thus supports the idea that opioid receptors are involved in the antinociceptive effects of HES (8). Therefore, the lack of reactivity for compounds with HP- $\beta$ -CD to such tests that imply the thermo-algesic mechanism could be explained by the lack of involvement in the mechanism dependent on opioid receptors located in the central nervous system, because these compounds have minimal access at this level. By inclusion in cyclodextrins, especially HP- $\beta$ -CD which has a high water solubility compared to  $\beta$ -CD, the HES-HP- $\beta$ -CD complex became less lipophilic than the HES- $\beta$ -CD complex, which caused a decreased crossing of the blood-brain barrier and implicitly a lack of reactivity during this tests.

#### **The constrictive abdominal response test**

This test is usually considered to be relevant to the pathogenesis of inflammatory pain, since no cell necrosis occurs and it allows the evaluation of central and peripheral analgesia (15).

**Table 3.** ED<sub>50</sub> values (mg/kg body weight/p.o) for samples analyzed by constrictive abdominal response test

Time	HES	HES- $\beta$ CD	HES-HP- $\beta$ CD
<b>60 minutes</b>	194.29 $\pm$ 55.68 TLC 28.24 – n/a	217.73 $\pm$ 67.86 TLC 113.38-1156.4	133.11 $\pm$ 36.93 TLC 75.5-306.84
<b>90 minutes</b>	220.11 $\pm$ 42.34 TLC 24.44-1300.18	223.34 $\pm$ 86.22 TLC 64.22-1021.45	128.34 $\pm$ 31.27 TLC 64.45 - 280.38
<b>120 minutes</b>	224 $\pm$ 26.22 TLC 48.22-1267.32	231.68 $\pm$ 51.84 TLC 3.38-1312.34	140.22 $\pm$ 38.54 TLC 44.52 - 342.84

TLC - True Confidence Limits,

n/a – not available

As seen in Table 3, all compounds showed antinociceptive action on the Zymosan chemical nociceptive model for the studied sequence of doses. The ED<sub>50</sub> values demonstrate a comparable action between free HES and HES- $\beta$ -CD, but inclusion in HP- $\beta$ -CD lead to superior potency.

The inflammatory response to administration of Zymosan is characterized by abdominal constriction response, plasma extravasation, leukocyte infiltration and biosynthesis of hyperalgesic eicosanoids (25). Moreover, it has been shown that inflammatory agents don't directly stimulate the release of primary hyper-nociceptive mediators, but this is in fact preceded by a cascade of cytokines that act simultaneously and synergistically (15, 16). Therefore, the antinociceptive action by chemical mechanism can be explained by inhibition of



proinflammatory mediators such as IL-1, IL-6, IL-8, TNF- $\alpha$  and PGE2.

#### **The Randall-Selitto test and inflammatory edema test**

The Randall-Selitto test allows the assessment of inflammatory pain by applying pressure to the inflamed area. The development of edema allows the evaluation of mechanical antinociceptive action (hyperalgesia produced by chemical stimulus and pressure stimulus) and of the anti-inflammatory action by measuring the paw volume.

**Table 4.** ED<sub>50</sub> values (mg/kg body weight/p.o) for samples analyzed by Randall-Sellito test and inflammatory edema test

Test	HES	HES- $\beta$ CD	HES-HP- $\beta$ CD
<b>Randall Selitto</b>	228.16 $\pm$	211.28 $\pm$	148.84 $\pm$
	66.23	43.27	41.64
	<i>TLC 122.61</i>	<i>TLC 113.38</i>	<i>TLC 35.23</i>
	<i>- 988.08</i>	<i>- 1156.4</i>	<i>- 886.42</i>
<b>Inflammatory paw edema</b>	200.80 $\pm$	188.86 $\pm$	160.22 $\pm$
	38.21	60.21	43.20
	<i>TLC 68.23</i>	<i>TLC 52.24</i>	<i>TLC 38.44</i>
	<i>- 1133.89</i>	<i>- 1123.15</i>	<i>- 880.26</i>

TLC - True Confidence Limits

The animals presented a significant reduction in pain perception for all administered samples. In both tests, the ED<sub>50</sub> values could be determined for all analyzed compounds.

HES- $\beta$ -CD compounds showed similar antinociceptive action to that of free HES, but a superior potency for the anti-inflammatory action.

HES-HP- $\beta$ -CD compounds showed superior potency for both types of actions compared to free HES and HES- $\beta$ -CD compounds, the antinociceptive action in inflammatory conditions being more relevant.

Cunha et al. demonstrated that s.c. administration of carrageenan into the plantar region in mice causes hyperalgesia by locally stimulating the production and release of inflammatory cytokines such as TNF- $\alpha$ , keratinocytes and IL-1 $\beta$ , which could represent the link between the release of primary hypernociceptive mediators and injury (26, 27). Moreover, carrageenan can trigger an acute inflammatory process involving the sequential release of pro-inflammatory mediators, especially histamine, serotonin, prostaglandins and thromboxanes (23).

Pinho-Ribeiro et al. demonstrated that HES reduces inflammatory pain and inflammation by suppressing cytokine production, NF- $\kappa$ B activity and oxidative stress (28). Thus, it is reconfirmed that the analyzed samples can reduce carrageenan-induced hypernociception by interfering with cytokine production. Furthermore, by inhibiting cellular influx of carrageenan and reducing

proinflammatory cytokines, the inflammatory process will be diminished.

The anti-inflammatory activity proved to be stronger when the complex was obtained using a more hydrophilic cyclodextrin (HP- $\beta$ -CD), which also lead to the formation of a more easily soluble complex. In this case, the involvement of the peripheral opioid system is important in clinical practice, the adverse effects of opioids on the central nervous system (e.g. respiratory depression or addiction) being suppressed or reduced (23).

#### **Conclusions**

Free HES has shown antinociceptive and anti-inflammatory activities on all studied models, with a higher potency for non-inflammatory nociceptive models by thermal stimulus (90-minute testing) compared to chemical stimulus. For inflammatory nociception and inflammatory edema models, the inhibition potency is comparable.

Inclusion compounds with  $\beta$ -CD showed a superior potency compared to free HES on non-inflammatory nociceptive models by thermal stimulus at 60 minutes, but not on chemical stimulus models. Moreover, for these compounds the potency was comparable for inflammatory nociception models and inflammatory edema model.

HP- $\beta$ -CD inclusion compounds had no activity on non-inflammatory nociceptive models by thermal stimulus. However, for non-inflammatory nociceptive model by chemical stimulus, inflammatory nociceptive model, and for inflammatory edema model, the potency was higher than that of  $\beta$ -CD inclusion compounds and of free HES.

In conclusion, the inclusion compounds showed superior potency compared to free HES. For HES- $\beta$ CD, the antinociceptive action in experimental models of non-inflammatory nociception by thermal stimulus prevailed, while for HES-HP- $\beta$ CD the antinociceptive action on models of non-inflammatory nociception by chemical stimulus, the antinociceptive action in inflammatory conditions and the anti-inflammatory action prevailed.

This research may be the starting point for future studies regarding the improvement of some pharmacological activities of HES through inclusion in CDs, so as to find better therapeutic options, which is of great importance in the pharmaceutical field.

#### **Author contributions.**

All authors had the same contribution.

**Conflict of interests.** The authors declare that there is not conflict of interest.

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## Access to post - stroke physical rehabilitation after acute reperfusion therapy– the neglected link in ischemic stroke management: a retrospective cohort study



WEB OF SCIENCE

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### Abstract

**Background:** The burden of stroke is high in Romania and data regarding access to post – stroke rehabilitation are almost non-existent. We aimed to determine the percentage of patients who benefited from post-stroke rehabilitation and to describe the most common rehabilitation settings.

**Methods:** A structured telephone-based questionnaire regarding access to post-stroke rehabilitation therapy and outcomes was administered to all patients with ischemic stroke who benefited from reperfusion therapy in a tertiary center in 2019.

**Results:** 211 stroke patients received reperfusion therapy during the studied period. Out of these, 208 patients were included in the initial analysis and 109 patients were deemed eligible for post-stroke rehabilitation therapy. 57 patients (55.8%) performed post-stroke rehabilitation. In-hospital rehabilitation was reported by 35 patients (32.1%) with a median length of hospital stay of 14 days. 28 patients (25.6%) performed home based physical therapy with a median frequency of 3 sessions per week. 12 patients (11.1%) were admitted to nursing homes. Compared to stroke patients who did not perform in-hospital rehabilitation, those who did were younger (median age 65 years vs. 73 years,  $p=0.01$ ) and more likely to have moderate-severe post-stroke disability (mRS score 3 – 5 at discharge 80% vs. 59.4%,  $p=0.03$ ). mRS score at discharge  $\leq 2$  was a significant predictor for not pursuing post-stroke rehabilitation ( $p < 0.001$ ).

**Conclusion:** Approximately 50% of the stroke patients treated with reperfusion therapies were eligible for post-stroke rehabilitation and approximately 50% of them had access to rehabilitation therapy while only 30% had access to in-hospital rehabilitation.

**Keywords:** Stroke rehabilitation; Eastern Europe; Romania; Rehabilitation Center; Physical Therapy,

### Introduction

As an overwhelming disease of huge medical, social and economic significance, stroke is now the second leading cause of disability and death worldwide.(1) Eastern Europe, where Romania is located, is the region with the second highest stroke incidence in the world, after east Asia, being estimated that around 30% of the adult population is at risk of suffering a stroke during their lifetime.(2,3) Despite this high stroke burden, this region reports overall low access to appropriate acute and post – acute stroke care and reperfusion therapies.(4) In order to offset the dramatic impact that a future increase in stroke prevalence is expected to have in Europe, a Stroke Action Plan for Europe (SAP-E) was recently developed. This paper emphasizes the importance of national stroke plans that should encompass an entire “stroke chain”, from primary prevention to life after stroke and also offers targets and guidance for every link in this chain.(5)

In order to provide equal access to proven effective therapies for all stroke patients, healthcare policy makers, public healthcare specialists and clinicians across the world should first analyse their existing individual

capabilities and unique infrastructure. Assessment of the existing status is a key reference point that should lead to the settlement of an interconnected stroke network rather than myopic singular stroke ready hospitals.(6) This implies focusing on every link in the stroke care chain starting from stroke awareness and ending with comprehensive rehabilitation and adequate post-stroke care.(5)

The 2006 Helsingborg declaration stated that all stroke patients in Europe should have access to appropriate rehabilitation by 2015.(7) However, in 2017 access to post - stroke inpatient rehabilitation was found to vary widely, the percentages of those actually benefiting from this therapy ranging from 15.1 to 44.3% in different European countries.(8) Access to post – stroke rehabilitation is expected to be low in Eastern Europe but available high – quality data on this subject are scarce or even non – existent for most of the countries from this region. Available published data shows unequal and scant availability of rehabilitation services. Moreover, post – stroke rehabilitation in Eastern Europe is usually focused



only on physical therapy, while access to occupational therapy, speech therapy and psychological care is generally lacking.(9)

The post - stroke care costs as well as the effectiveness of rehabilitation are dependent on the quality of rehabilitation services available for each stroke patient. Early supported discharge services with multidisciplinary coordination reduce in-hospital stay, long-term dependency and increase the proportion of stroke patients living at home.(10) European National healthcare systems should strive to adhere to SAP-E recommendations, aiming to build adequate post - stroke rehabilitation systems capable of providing: (1) access to appropriate rehabilitation for 90% of stroke patients and (2) early supported discharge for at least 20% of stroke patients. Data concerning post - stroke access to rehabilitation across Eastern European countries are currently collected by the Registry of Stroke Quality (RES - Q) endorsed by the European Stroke Organisation - East Programme.(11) However, by capturing mainly data regarding access to early supported discharge, this registry underreports overall access to post - stroke rehabilitation as waiting times between initial hospital discharge and admission in a Department of Rehabilitation or first evaluation by a specialist in rehabilitation therapy can be rather long in many Eastern European countries.(12)

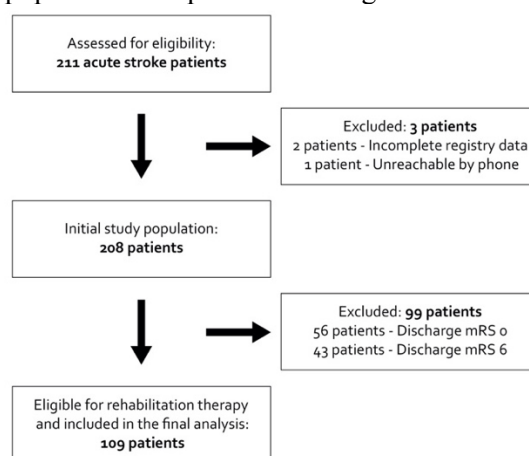
Romania provides publicly - funded healthcare to all citizens, including hospitalization for rehabilitation therapy. Post - acute in - hospital rehabilitation for stroke patients takes place in designated wards or hospitals after discharge from a Stroke Unit or Department of Neurology. Public nursing homes are scarce and therefore patients are usually admitted to private nursing homes. In an attempt to support the long - term care of stroke survivors, the Romanian authorities offer a monthly allowance on the basis of the degree of disability which can be used to partially cover the expenses of private nursing homes or rehabilitation in private settings.

The aim of this study was to determine the access to post - stroke rehabilitation therapy and to describe the setting of rehabilitation in a population of patients with acute ischemic stroke treated by intravenous thrombolysis and/or mechanical thrombectomy in the University Emergency Hospital Bucharest.

## 2. Materials and Methods

All stroke patients treated by intravenous thrombolysis (IVT) and/or endovascular procedures (EVT) in the University Emergency Hospital Bucharest between 01.01.2019 and 31.12.2019 were screened for eligibility to be included in this study. Informed consent for scientific and clinical studies was signed by the patients and/or their caregivers at admission and all patients were included in the local database of the Romanian Registry

for Interventional Treatment in Acute Stroke (RRIT-AS). This database includes prospectively collected data on all ischemic stroke patients who receive reperfusion therapy at admission. Patients were excluded from the study if: (1) they were discharged with a modified Rankin score (mRS) of 0 or 6; (2) registry data was incomplete (3) they or their caregivers refused to participate in this study during the telephone interview (4) they or their caregivers were unreachable by phone. The flow diagram of the study population is represented in Figure 1.



**Figure 1.** Diagram of the study population.

A structured questionnaire was developed and administered to patients or their caregivers by telephone interview by two experienced stroke neurology residents B.C and I.E between 01.07.2020 and 15.07.2020. The questionnaire aimed to answer the following questions: (1) Which was the mRS score at the time of telephone contact?; (2) Was the patient living at home or in a nursing home?; (3) Did the patient benefit from rehabilitation services provided by a rehabilitation institution after their discharge?; (4) If the patient benefited from rehabilitation in an institution, was there any delay between discharge from the Neurology Department and admittance to the rehabilitation institution?; (5) If the patient benefited from rehabilitation in an institution, how many times was the patient hospitalized in the institution?; (6) If the patient benefited from rehabilitation in an institution, which was the length of hospital stay there?; (7) If the patient benefited from rehabilitation in an institution, was the patient hospitalized in a private or public rehabilitation institution?; (8) If the patient didn't benefit from rehabilitation, which was the reason?; (9) Did the patient benefit from rehabilitation at home?; (10) If the patient benefited from rehabilitation at home, was it supported by public health insurance or by personal funding?; (11) How many times a week did the patient receive rehabilitation services at home?; (12) Was the patient granted a degree of disability and corresponding allowance?; (13) Did the patient receive an attendant allowance? The simplified mRS questionnaire was



translated into Romanian and used as the reference questionnaire for obtaining the mRS score of the patients.(13) Access to rehabilitation was defined as access to any kind of rehabilitation. Rehabilitation institutions were considered all public or private hospitals providing rehabilitation services as in-patient care. The mean number of days spent in the rehabilitation institution and number of admissions were recorded separately during the interview for each patient.

Clinical data and demographic data were extracted from the local database of the RRIT-AS and linked to the survey data. Initial stroke severity was classified according to the National Institute of Health Stroke Scale (NIHSS). Short - term stroke outcome was defined as outcome at the moment of hospital discharge and was assessed with the mRS score. Patients with mRS scores 0 - 2 were considered functionally independent. Both mRS and NIHSS scores were assigned by attending physicians during hospitalization and included in the Stroke Registry after patient discharge. Traditional risk factors analysed in this study were defined as follows: (1) diabetes mellitus: clinical history of diabetes mellitus or glycated haemoglobin  $\geq 6.5\%$  or random plasma glucose of  $\geq 200\text{mg/dl}$  or fasting glucose level  $\geq 126\text{mg/dl}$ ; (2) dyslipidaemia: low density lipoprotein cholesterol  $\geq 100\text{mg/dL}$  or triglycerides  $\geq 150\text{mg/dl}$  or previous treatment with a statin; (3) arterial hypertension: history of systolic blood pressure  $\geq 140\text{mmHg}$  and/or diastolic blood pressure  $\geq 90\text{mmHg}$  on two separate occasions or persistently elevated blood pressure during hospitalization or prior antihypertensive treatment; (4) coexistent cardiovascular disease: history of ischemic heart disease and/or diagnosis of ischemic heart disease and/or history or diagnosis of peripheral artery disease; (5) previous stroke: clinical history of stroke (silent lesions found on CT were not taken into consideration). (6) major cognitive decline: history of pre - stroke dementia. Stroke aetiology was assessed in accordance with Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.(14)

All statistical analyses were performed using NCSS 12 Statistical Software (NCSS, LLC. Kaysville Utah, USA) and Medcalc Statistical Software 18.11.3 (Medcalc Software, Ostend, Belgium). Statistical analysis was limited to bivariate analysis due to the small sample size. A pre-set significance level of  $p < 0.05$  was considered statistically significant for all comparisons. Continuous variables are described as mean  $\pm$  standard deviations (SD) or median and 25 - 75 IQR and categorical variables as absolute numbers and percentages. For comparison between continuous variables, Mann - Whitney or Kruskal Wallis test were used, according to the number of selected variables. Chi-squared test and Fisher's exact test were used for testing the strength of association between categorical variables.

### 3. Results

A total number of 211 stroke patients were treated by IVT/EVT in 2019 in our hospital. 3 patients had incomplete registry data or were unreachable for the telephone interview so that the initial study population included 208 patients. Since 99 of the 208 patients had discharge mRS scores 0 or 6 and were considered non - eligible for rehabilitation therapy, 109 patients were included in the final analysis of this study. The clinical and demographic characteristics of these patients are listed in Table 1.

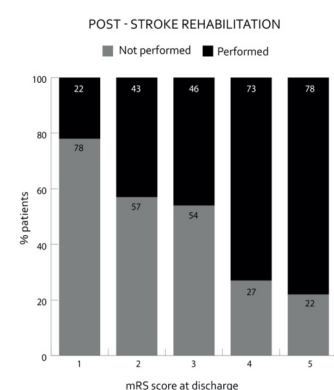
57 patients (52.3% of the stroke patients deemed eligible for rehabilitation therapy or 27.4% of the stroke patients initially included in the study) reported to have performed any kind of rehabilitation (including: in-hospital rehabilitation, outpatient rehabilitation, physical rehabilitation at home, physical rehabilitation in the nursing home). The setting of rehabilitation procedures is detailed in Table 2.

In-hospital post - stroke rehabilitation after discharge from our department was reported by 35 patients (32.1%), with a median length of stay per hospitalization of 14 days (Range: 7 - 60 days). Out of these patients, 18 (51.4%) were admitted for in - hospital rehabilitation one time, 7 patients (20%) two times, 4 patients (11.4%) three times and the remaining were admitted four or more times. 29 (82.8%) of these patients benefited from rehabilitation in a public hospital, 4 (11.4%) in a private hospital and 2 (5.7%) opted for both private and public hospital admissions. There was no statistically significant difference between the number of in - hospital rehabilitation admissions for patients hospitalized in our department in the first or last 6 months of 2019 (mean 2.57 vs 1.81 times,  $p = 0.1$ ). 29 (82.8%) of the 35 patients who performed in - hospital post - stroke rehabilitation benefited from early supported discharge, while 6 (17.2%) were admitted to the rehabilitation facility in the first weeks after the discharge from our department. 14 patients (40%) of those who benefited from in-hospital rehabilitation continued physical therapy at home. As compared to stroke patients who did not perform in - hospital rehabilitation, those who did were younger (median age 65 years vs. 73 years,  $p=0.01$ ) and more frequently had moderate - severe post - stroke disability (mRS score 3 - 5 at discharge 80% vs. 59.4%,  $p=0.03$ ). Physical therapy at home was reported by 28 patients (25.6%). Out of these patients, 14 (50%) performed rehabilitation only in this setting, while the others were first admitted for in - hospital rehabilitation and then continued rehabilitation therapy at home. The median period of performing rehabilitation procedures at home was 3 months (25 - 75 IQR: 2 - 7.7 months) and the median frequency of sessions was 3 times per week (25 - 75 IQR: 2 - 4 times/week). Only 7 patients (25%) of those who reported physiotherapy at home applied for

and received public reimbursement of the home - based physical therapy.

Out of the 109 patients included in the final analysis, 12 (11.1%) were admitted to a nursing home at any time after discharge from our department. All nursing homes were private facilities and caregivers reported that they offered at least physical therapy to their patients.

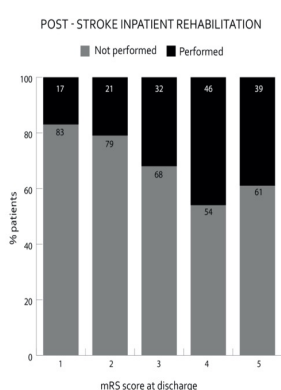
66 patients (60.5%) did not undergo in-hospital rehabilitation and were not admitted to nursing homes. The most frequently reported reasons for not accessing inpatient rehabilitation were: 1) patients thought they don't need it (31 patients, 46.9%), 2) patients didn't want to go to rehabilitation (11 patients, 16.6%), 3) patients didn't know that they should go to rehabilitation (6 patients, 9.1%). Other less frequently mentioned reasons for not pursuing rehabilitation were: couldn't afford rehabilitation, were not suitable candidates for rehabilitation due to other severe medical illnesses.



**Figure 2.** Access to post – stroke rehabilitation in the study population

A low mRS score at discharge was a significant predictor for not pursuing post-stroke rehabilitation ( $p < 0.001$ ). 37 patients (33.9%) were discharged with an mRS score of 1 or 2 points. 7 of them (18.9%) reported having benefited from in-hospital post-stroke rehabilitation and 3 of them (8.1%) from physical therapy at home, while the other 26 (70.2%) did not pursue post – stroke rehabilitation in any setting. The most frequently reported reasons for not pursuing rehabilitation in patients discharged with mRS scores 1 – 2 were: 1) considered it was not needed (90.91%) and 2) didn't want to perform it (4.55%). 72 patients (66.1%) were discharged with mRS scores 3 – 5. 28 of these patients (38.9%) performed in – hospital rehabilitation, 11 (15.2%) performed only physical procedures at home, 7 patients (9.7%) were admitted to a nursing home, while 26 (36.1%) of them did not perform post – stroke rehabilitation. These results are detailed in Figures 2 and 3.

By the time of the telephone interview, 22 (20.02%) of the patients included in the final analysis died. Eleven patients (10.1%) died after discharge without benefiting from any post-stroke rehabilitation: 4 (3.6% of the study



**Figure 3.** Access to in-patient rehabilitation in the study population

population) had an mRS score of 2 at discharge and reported that they did not consider rehabilitation necessary, while the remaining 7 (6.4%) reported either that they couldn't afford it or that they didn't know that post-stroke rehabilitation was an option or they died before being admitted to rehabilitation.

Out of the 87 patients who were alive at the time of the survey, 26 (29.9%) applied for and received disability allowances and 14 (16.1%) received a supplementary allowance to support the payment of a personal caregiver.

#### 4. Discussion

The population of this study consisted of patients with acute ischemic stroke who benefited from reperfusion therapies in accordance with national and international guidelines.(15) Stroke outcome after IVT/EVT is usually assessed at three months after the cerebrovascular event. According to different meta - analysis and trials, 43.5 – 55% of patients achieve functional independence (mRS scores 0-2) by this time.(16–18) However, studies performed in healthcare systems with limited resources have shown that stroke patients from these countries generally have worse outcomes than those reported in landmark papers, probably due to multiple factors, including quality of acute stroke care and access to rehabilitation therapies.(19) This finding emphasizes that stroke care is a continuum and post-stroke rehabilitation should accompany acute stroke therapies.

Recent estimates for Europe suggest a 27% percent increase in the demand for rehabilitation and long - term care services after stroke by 2047. An East – West gradient of increasing stroke burden is expected to affect European countries in the future. This gradient is most probably attributable to insufficient and ineffective strategies of primary stroke prevention and below – standard quality of acute and long – term stroke care in many Eastern European countries.(20) Given the presumed low – access to adequate stroke care in the region, healthcare policymakers should work together and focus on proven disability – reducing therapies such as admittance to stroke units, thrombectomy, thrombolysis and early supported discharge to rehabilitation services.(21)

According to the Stroke Alliance For Europe (SAFE) report, the percentage of patients that have access to post stroke rehabilitation widely varies from 25% to 60% in the Eastern European countries for which data on this subject is available.(9) However, these data are frequently based on surveys among key opinion leaders and papers that are usually more than ten years old and rarely on epidemiological studies or database inquiries. Romania is listed in the SAFE report with 30% of stroke patients having access to post-stroke rehabilitation in 2005/2006 and a subsequent paper regarding stroke care in Eastern Europe from 2012 states that efforts are being made to create neuro – rehabilitation units in Romania.

(22,23) Our results show that in the probably best available scenario, as most of the study population resides in Bucharest, the capital and the most developed city of the country, only 27.4% of the stroke patients included in this study benefited from this much needed therapy. The comparison of this percentage with the one reported by SAFE would lead to the conclusion that during the past 15 years access to post – stroke rehabilitation in Romania remained unchanged or has actually worsened, which definitely cannot be true.

In-hospital rehabilitation is the most standardised and well-defined type of post – stroke rehabilitation and therefore the most suitable for being analyzed in studies comparing efficacy and access to this therapy. In our study population, 21.2% of the stroke patients discharged alive had access to in – patient rehabilitation therapy, a percentage that is significantly lower than that reported by other countries.(8,24)

In order to improve access to rehabilitation for stroke patients and to adhere to European standards, Romania and other Eastern European countries should first focus on obtaining and analysing reliable data regarding their current status, which would probably be very similar to Brazilian estimates that more than 70% of patients do not have access to any kind of post stroke rehabilitation.(25) These data should include quantitative and qualitative parameters that would facilitate further comparisons between Eastern and Western European countries and ultimately determine clinical effectiveness. For example, a higher number of patients are being transferred directly to post stroke rehabilitation facilities in Sweden than in Latvia, which probably implies better stroke outcomes regardless of the total percentage of patients who have access to post-stroke rehabilitation. Moreover, while in Romania and Latvia patients usually spend around two weeks in rehabilitation facilities, they spend a far longer time in Sweden or in Poland, which may also impact the stroke outcome.(12,26)

Current recommendations state that all stroke patients should be evaluated by rehabilitation specialists in order to identify any “rehabilitation potential”. However, even some high income countries, such as Australia, report that less than 50% of the patients are being evaluated for scheduling the type of post-stroke rehabilitation during their stay on stroke units.(27) In lower – income countries this percent might be far worse. In our study, a minority of patients were evaluated by a rehabilitation specialist during hospital admission. The implementation of neuro- rehabilitation wards dedicated to stroke and other specific neurological diseases could facilitate the early evaluation of this category of patients and could improve the collaboration between neurologists and rehabilitation specialists with the ultimate goal of increasing the number of stroke patients benefiting from rehabilitation therapy.

Patients and caregivers’ awareness regarding post – stroke rehabilitation was poor in our study population. A significant percentage of those who did not benefit from this therapy reported that they “thought they didn’t need rehabilitation therapy”, they “didn’t know that they should undergo rehabilitation therapy” or they “didn’t want to perform rehabilitation therapy”. Frequently overlooked in the setting of emergency hospitals, detailed discussions between neurologists, rehabilitation specialists and stroke patients or caregivers during hospitalization for acute care might change the perspective of patients who state that they “don’t want” to perform rehabilitation procedures, thereby improving stroke outcome.(28)

Our study population consisted of all stroke patients treated by IVT/EVT during one year. We considered that this population was “the best – case scenario” for our country since patients who receive reperfusion therapies tend to be younger, have more severe strokes and a higher likelihood of pre-stroke independence (15,24), which makes them suitable candidates for post – stroke rehabilitation. However, the selection on the basis of this criteria is also a major limitation of our study due to the lack of external validity to a general stroke population. Nevertheless, the low number of patients benefiting from in – hospital rehabilitation in this “best case scenario”, should act as an incentive to enhance cooperation between neurologists and rehabilitation specialists in order to achieve European targets regarding rehabilitation therapy designed for all stroke patients.

Another significant drawback of our study was the variable length of follow-up. A trend towards more frequent admissions for in – hospital rehabilitation could be observed for patients discharged in the first 6 months of 2019 as compared to those discharged in the last 6 months of 2019. A future study with prospective collection of data regarding post – stroke rehabilitation therapy at pre – specified time points after acute hospital care is definitely needed in Romania.

**5. Conclusion** In our cohort of acute ischemic stroke patients who benefited from reperfusion therapies, 51.6% were likely candidates for post – stroke rehabilitation but only 27.4% actually accessed this much needed therapy. 16.8% of the study population benefited from post – stroke rehabilitation in an inpatient setting. Approximately two thirds of our stroke patients discharged with mRS scores of 1 – 2 and one third of those discharged with mRS scores of 3 – 5 did not perform any type of rehabilitation therapy. Access to post – stroke rehabilitation was poor in our cohort. The real situation is probably worse throughout the country and therefore an urgent action to improve access of stroke survivors to rehabilitation therapy is needed.



## Conflicts of interest and Ethics

The authors declare no conflict of interest.

## Institutional Review Board Statement:

Ethical review and approval were waived for this study, due to the fact that the National Stroke Registry was approved by the relevant Ethics Committee and patients provided written informed consent for inclusion in the National Registry and for the subsequent data use. Informed consent was obtained from all subjects or caregivers involved in the study.

## Author Contributions:

Conceptualization of the study R.A.R and E. O.T; Methodology E.O.T; Data Curation: B.C, I.E, C.G, Writing – original draft: R.A.R; Writing -review and editing: R.A.R, E.O.T, C.T; Supervision. C.T; Funding acquisition: CT; All authors have read and agreed to the published version of the manuscript.

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**Table 1.** Clinical and demographic characteristics of the study population

	<b>Overall (n=109)</b>	<b>Performing post – stroke rehabilitation (n=57)</b>	<b>Not performing post – stroke rehabilitation (n=52)</b>	<b>p - value</b>
<b>Demographics</b>				
Age (years), median	71 (62 – 79)	70 (57 – 78)	72 (63 – 80)	0.1
Female Sex, %	56 (51.4%)	30 (52.6%)	26 (50%)	0.7
Urban area, %	81 (74.3%)	46 (80.7%)	35 (67.3%)	0.1
<b>Comorbidities &amp; Risk Factors</b>				
Arterial Hypertension,%	67 (61.5%)	34 (59.6%)	33 (63.5%)	0.6
Dyslipidaemia, %	65 (59.6%)	36 (63.2%)	29 (55.7%)	0.4
CV disease,%	15 (13.7%)	10 (17.5%)	5 (9.6%)	0.6
Diabetes mellitus, %	23 (21.1%)	9 (15.8%)	14 (26.9%)	0.1
Atrial fibrillation, %	23 (21.1%)	12 (21.1%)	11 (21.2%)	0.9
Prior stroke, %	17 (15.6%)	7 (12.3%)	10 (19.2%)	0.3
Prior major cognitive decline,%	2 (1.8%)	0	2 (3.8%)	0.1
<b>Stroke - related characteristics</b>				
Stroke territory				0.9
Left carotid	57 (52.3%)	29 (50.9%)	28 (53.8%)	
Right carotid	39 (35.8%)	21 (36.8%)	18 (34.6%)	
Vertebro-basilar	13 (11.9%)	7 (12.3%)	6 (11.5%)	
Admission NIHSS, median	16 (8-21)	17 (10-22)	11 (6.2 – 9.7)	<b>0.008</b>
Initial stroke severity				<b>0.01</b>
Mild stroke <8	25 (22.9%)	8 (14%)	17 (32.7%)	
Moderate stroke 8-16	37 (33.9%)	18 (31.6%)	19 (36.5%)	
Severe stroke >16	47 (43.2%)	31 (54.4%)	16 (30.8%)	
Discharge NIHSS, median	5 (2-13)	9 (3.5 – 4.5)	3 (1-6)	<b>&lt;0.001</b>
Stroke severity at discharge				<b>&lt;0.001</b>
Mild stroke <8	65 (59.6%)	22 (38.6%)	43 (82.7%)	
Moderate stroke 8-16	30 (27.5%)	26 (45.6%)	4 (7.7%)	
Severe stroke >16	14 (12.9%)	9 (15.8%)	5 (9.6%)	
Discharge mRS, median	3 (2-4)	4 (3-4.5)	2.5 (1-3)	<b>&lt;0.001</b>
Discharge mRS, %				<b>&lt;0.001</b>
mRS scores 1-2	37 (33.9%)	11 (19.3%)	26 (50%)	
mRS scores 3-5	72 (66.1%)	46 (80.7%)	26 (50%)	
Follow-up mRS, mean ± SD	3 (1-5)	3 (2-5)	2 (1-3.7)	<b>0.009</b>
Follow-up mRS categories, %				0.07
mRS scores 0-2	46 (42.2%)	19 (33.3%)	27 (51.9%)	
mRS scores 3-5	41 (37.6%)	27 (47.4%)	14 (26.9%)	
mRS score 6	22 (20.2%)	11 (19.3%)	11 (21.1%)	
Thrombolysis, %	88 (80.7%)	45 (80.3%)	43 (82.7%)	0.7
Thrombectomy, %	29 (26.6%)	21 (36.8%)	8 (15.4%)	<b>0.01</b>
<b>Stroke etiology by TOAST criteria</b>				
Cardioembolic	48 (44.1%)	26 (45.6%)	22 (43.1%)	0.7
Large artery disease	24 (22%)	12 (21.1%)	12 (23.5%)	
Small vessel disease	-	-	-	
Other etiology	2 (1.8%)	1 (1.7%)	1 (1.9%)	
Undetermined etiology	35 (32.1%)	18 (31.5%)	17 (33.33%)	

CV: Cardiovascular disease; Follow – up mRS: as obtained at the time of interview; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Score; ONT: Onset to needle time; TOAST: Trial of ORG 10172 in Acute Stroke Treatment;

**Table 2.** Setting of rehabilitation therapy for the study population (n=109 patients)

<b>Type of rehabilitation</b>	<b>Number of patients</b>	<b>%</b>
Only physical therapy at home	14	12.8
Only in – hospital rehabilitation	18	16.5
In-hospital rehabilitation + physical therapy at home	13	11.9
In-hospital rehabilitation + nursing home	3	2.7
In-hospital rehabilitation + nursing home + physical therapy at home	1	0.9
Nursing home + physical therapy at home	0	-
Only nursing home	8	7.3
<b>Total benefiting from physical therapy at home at any time post – discharge</b>	<b>28</b>	<b>25.6</b>
<b>Total benefiting from in-hospital rehabilitation</b>	<b>35</b>	<b>32.1</b>
<b>Total benefiting from admission in a nursing home</b>	<b>11</b>	<b>11</b>



## Quantifying the functional diagnosis in the rehabilitation of postural problems of biomechanical junior female players in table tennis



WEB OF SCIENCE

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### Abstract

We have lived in an era in sports history in which due to the intensity of the confrontations between athletes, disorders manifested by headaches, shoulder, pelvis and knee aches etc. appear more often. The performers during puberty require special attention on their morpho – functional development from the kinesiologist who is part of the multidisciplinary team, due to many transformations of the human body specific at this age category. 13 juniors female athletes have participated to the study, being assessed anthropometric, plantar pressures and posture with software FreeStep by Sensor Medica, biomechanical analysis and from technical & tactical point of view by 5 tests with DartFish 360S. Within the statistical – mathematical analysis, we have used Pearson correlation coefficient which favoured the identification of the strongest correlations resulted from the technical – tactical - anthropometric – plantar pressures and postural unbalances ( $r > 1.00$  at test 1 and  $r > 0.84$  at test 2). Assumption: It is assumed that by using established methods and means to assess postural deficiencies and to assess the level of consolidation of the topspin attack, we can identify the correlations between them which would facilitate the creation in the future of an efficient postural improvement program. The goal is to improve the quality of life and sports performance in junior female table tennis players. The conclusions of this study demonstrate the fact that the mobility of the spine in frontal plan, high thoracic elasticity and an increased lateral mobility on the opposite side of the active arm represent advantages intended to optimize the attack by topspin, while the supraponderability, the pain in lumbar area and the shoulder's asymmetry constitute disruptive factors of attack's performance.

**Keywords:** *plantar pressures, postural unbalances, baropodometric platforms, topsin attack efficiency, dartfish 360s,*

### Introduction

In order to perform in table tennis, it is necessary for the debut in sports training to be made around the age of 6-8 years old, a context in which repetitive, speedy unilateral movements can create postural deficiencies over time. This limits the training process aimed at meeting the performance objectives, while the early identification and implementation of methods and means meant to improve their problems are a "must have" for continuity and for the optimization of the performance capacity.

According to the results obtained in a research conducted on the basis of an opinion survey applied to table tennis specialists dealing with sports training, a program for evaluating and improving incorrect body positions could bring benefits in improving the attack by topspin, aspect voted unanimously. By identifying the factors that can improve the performance in table tennis, such as biomechanics and posture, we will be able to provide information for the athletes involved in profile competitions, but also to provide guidance for a physical activity performed without repercussions on the osteo-articular and muscular level among the devotees practicing this discipline during free time [1].

By analyzing the hitting mode using the topspin technical-tactical element executed on both sides, the specialists observed that the forehand strokes mainly use the motion of trunk axial rotation, shoulder flexion, and shoulder internal rotation to produce racket linear velocities [2], while for backhand strokes, it primarily involves shoulder external rotation and flexion, elbow extension, forearm supination, and wrist extension [3]. In table tennis, the level of technical expression in the game is an essential factor for the athletes involved in high performance, an adequate execution technique translated by a high-performance biomechanics, meaning that you can perform coordinated physical actions, executed with adequate power and ability to imprint to the ball an effect and a speed adapted to the situation on the play field, according to the same authors, a high level of technical training implying an optimal orientation of the process in the context of the exchange of balls within a point disputed in the set's register, i.e. the adversary must not detect the intent of the technical expression [4].

The opponent has less opportunity to hit an offensive stroke against a ball with higher speed and greater spin

[5]. The topspin forehand is one of the most attacking shots in table tennis. In a recent study, Yoichi I. et al. found that it was used more often in winners than other stroke types, suggesting that mastering this shot is critical to winning matches [6].

An interesting aspect regarding the game tactics at the level of women's table tennis compared to the men's is given by the differences identified regarding the acceleration achieved at the execution of the attack using the topspin technical-tactical element from the ball with backspin effect, which highlights the fact that female tennis players use topspin on both hitting sides, while male tennis players look for opportunities to execute strong shots with the forehand topspin on the whole table [7].

Modern table tennis is a sports game that demands high speed in all forms of manifestation, variation, complexity and a quick response to various changing stimuli, the difficulty of this sports discipline being accentuated by the speed of movement and by the different effects imprinted on the ball. It is obvious that the forehand topspin is among the most used blows both in attack and in counter-attack, the speed of movement of the paddle when in contact with the ball reaching 20 m / s, after the hit, the ball will travel with 45m / s, the effect imprinted on it causing a rotation of 140 r / s, both theoreticians and practitioners considering that the forehand topspin is a complex hit involving a kinematic chain in which there is a cycle of elongation and muscle contraction, the speed with which the paddle hits the ball being initially influenced by the coxo-femoral joint and by the rotation of the trunk, followed by the flexion and adduction made at the scapulo-humeral joint level and the flexion of the forearm on the arm [8].

In the technical and physical context presented above, according to Dellaporta, et al., trunk flexion, extension, rotation and the time spent in the basic position, specific to the training and playing activity of table tennis players, facilitate a vulnerability of the lumbar area, causing pain [9].

Professional players focus on attack and most players who are participating in international competitions use the forehand topspin loop to create high spin and speeds on the ball. Moreover, because of making the size of the ball bigger for decreasing rate of the game, the force imposed on shoulder girdle muscles of table tennis players has been increased [10].

Muscle asymmetries, excessive curvatures of the spine and scoliosis are the factors that lead to painful syndromes, degenerative states, implicitly to disorders of motor functions, which can be disruptive factors in the efficiency of forehand and backhand topspin technical-tactical procedures mention that the dynamic stresses of the postural control require active contributions of the kinematic chain in order to develop a model of movement

with greater coordination, reason for which the posture represents an important aspect for the efficient execution of the topspin attack, being related to it the capacity to train and to limit the pain of the sportswomen, appeared at the level of the spine in case of its deficiency, generated by the vicious positions and unilateral repetitive movements in speed regime [7][11]. According to Iordan, D.-A., et al., after applying the survey, 52% of the coaches interviewed and involved in the training of the female juniors mentioned that the topspin is responsible for the occurrence of pain in the lumbar spine [12].

According to Filipcic, et al., in tennis, the asymmetry of the body is present starting with the youngest age category, an aspect that creates problems at spine level [13]. In table tennis, over-training, improper execution of the first part of training, the incorrect posture, the lack of concentration and emotional instability favour the occurrence of injuries [14].

For a physical development, beneficial to children, it is necessary to individualize by using specific devices of physiotherapy and physiotherapy [15,16].

To turn a research in postural area to value, it is necessary to implement the baropodometric analysis according to Rosário, which recommends the use of plantar orthoses to improve the painful conditions related to the lower limbs and the spine [17-18].

The maximum pressure of the support base is found in three points: at the level of the first metatarsal (hallux), of the lateral edge of the plant and of the calcaneus [26].

According to Stan,. the positive correlations resulting from the study on "Relationships between the pressures exerted by the sole of the foot and the distribution of muscle forces at trunk level", using the baropodometer and the Trunk Muscle Assessment System consisting of 4 components (a metal frame, a force transducer, a laptop and the software program for collecting, transmitting and processing the data collected by the translator), demonstrate the validity and efficiency of the system for measuring the muscle forces in the trunk, its every movement increasing the values of the pressure points at plantar level [19].

By using simple observation up to sophisticated analysis devices, we can evaluate lumbar lordosis and postural alignment, the services of a specialist had been used for the identification of these deviations [20,21,22]. Based on a study conducted by Negulescu, et al., the multiple twists of the trunk in high speed, specific to the topspin by forehand (the most prolific technical-tactical element, aspect scored by 50% of the surveyed coaches), create pain and disorders of the spine in the case of the female juniors involved in performance sports [23].

Following those mentioned in this introduction, it is necessary to monitor and evaluate athletes consistently [24] and we consider that anthropometric examination,

the plantar, postural analysis and the technical-tactical tests, along with the means associated to it, are determining factors in diagnosing the posture disorders and in creating programs to improve the quality of life of female athletes and to optimize the female junior table tennis players' performance [25].

## **Material and method**

### **Participants**

In this preliminary research, 13 junior female table tennis players involved in performance sports have been assessed (having experience in competitions of approximately 5.2 years, the average age being 12 years old, the height of 169.6 cm. and weight of 58 kg.), members of A.C.S. ACTIV Galați, L.P.S. Slatina, A.C.S.O.V. Bucharest Clubs. Within the previously mentioned club, the antropometric dimensions of the female players and the technical and tactical consolidation level of the attack by topspin had been measured, the postural assessment being made at the integralist medicine clinic named „Sănătate cu Ozon [Health by Ozone]” located in Galați City, 118 Domnească Street. The collected data had been processed and interpreted within the Kinetotherapy Research Centre of the Faculty of Physical Education and Sports within “Dunărea de Jos” University of Galați. In what concerns the participation to this study, we have selected only female subjects, performance junior players in table tennis with a good health state at the moment of performing the assessments which we are going to list below.

### **Procedures**

In order to reach the purpose of this scientific endeavour, we have used modern methods and means specific to kinesiotherapy, clinical medicine and table tennis, intended to highlight by assessment the most important aspects necessary for obtaining data of interest to the research team. They had been selected in accordance with the actual research level, their capacity to supply as many objective data as possible, the number of subjects, the time necessary for the assessment and the usage costs. At the assessment of the involved subjects, we had used the following methods, research means and technical and tactical assessment tests: *Anthropometric examination* – it has as purpose the assessment of the level of increasing the physical development degree [26]; *Schober Test* – it measures the muscular – articular mobility in flexion and extension movements of the trunk [19]; *“Finger to floor” test* – it assesses both the degree of mobility of the spine through the flexion movement of the trunk, and the mobility of the coxofemoral joints and the suppleness of the hamstring and gastrocnemius muscles. (Cordun, 2009) [27]; *“The Laterality Test”* – it assesses the lateral mobility of the trunk [28]; *Dynamometry* – it is measured and recorded the maximum force (in kg) of the palmar flexors in the right and left hand [19,26], being

performed with the Hydraulic Dynamometer of SH5001 type; *Computer software for analyzing the plantar pressures* (baropodometry freeMed) and the posture (images) – *FreeStep* by Sensor Medica.; *Computer software for biomechanical analysis, DartFish 360s*, being used for the biomechanical analysis of technical – tactical procedures used in the case of above mentions tests used for the assessment. This program was used in a scientific research by Mocanu & Negulescu, on the biomechanics of the attack by topspin in female junior table tennis players [29] in order to identify the efficiency of the movement, this being correlated with the execution technique [30].

For the evaluation of the level of consolidation of the attack by topspin, we have used a series of 5 *technical – tactical tests*, performed both with forehand and backhand, both diagonally and in line, as follows:

*P.1. Topspin with diagonal forehand performed from blockage.* This test that we have used to evaluate the level of consolidation of the topspin attack in the female juniors involved in our scientific endeavour was performed by diagonal forehand topspin from the no-spin ball, from blocking the game partner. \*The testing was performed using a number of 5 balls.

*P.2. Topspin with diagonal backhand performed from blockage.* This test that we have used to evaluate the level of consolidation of the topspin attack in the female juniors involved in our scientific endeavour was performed by topspin diagonal backhand from the no-spin ball, from blocking the game partner. \* The testing was performed using a number of 5 balls, counting each success.

*P.3. Diagonal Butterfly performed from blockage.* The Butterfly test from the no-spin or spin ball is made by sending the ball diagonally or only in line, using a certain procedure or technical procedures, aspect established from the beginning of the theme (e.g. while one of the players performs topspin on both sides diagonally, the other player sends the ball back in line, with blockage). In the case of the assessment on the level of consolidation of the topspin attack in female juniors III, the forehand and backhand topspin executed from the no-spin ball sent diagonally was evaluated, the return being made from the blockage made by the game partner [31]. \* We used a number of 5 balls, counting each successful ball exchange.

*P.4. Line Butterfly performed from blockage.* Regarding the level of consolidation of the topspin attack at this age category, we used the forehand and backhand topspin performed with no-spin ball sent in line, the return being made from the blockage made by the game partner [31]. \* The testing was performed in a number of 5 series in which each successful ball exchange was counted.

*P. 5. Multiball (topspin with forehand + topspin with backhand performed diagonally from no-spin ball,*



followed by the same technical procedures achieved from backspin ball). According to Mocanu, multiball training is a modern training method similar to the “ball robot” which is performed by the coach and a female athlete, involving a large number of balls, performed in order to make more efficient the technical-tactical procedures and to optimize the specific motor skills [26]. The “box” (the popular name of the above-mentioned method, specific to table tennis) is made as follows: the player who performs the topspin attack will have to execute from both sides of the table the topspin with forehand and topspin with backhand, the hits being sent only diagonally, first from the no-spin ball, followed by the same technical procedures performed from the backspin ball. This test in our case aims to assess the level of consolidation of the forehand and backhand topspin attack from the no-spin ball and from the backspin ball. \* We used for evaluation 10 series of 4 balls each (hit alternately with the forehand and then with the backhand) which were counted as successful only when the female athlete hit all 4 balls efficiently (they passed over the net, landing in the opponent’s court).

**The statistical – mathematical analysis** of the data obtained from the (topspin) technical – tactical and kinesiotherapeutic assessments had been interpreted by using *Microsoft Excel*.

The calculation formula for *Pearson* correlation coefficient achieved with the help of *Correl* function is:

$$Correl(X,Y) = \frac{\sum (x-\bar{x})(y-\bar{y})}{\sqrt{\sum (x-\bar{x})^2 \sum (y-\bar{y})^2}}$$

## Results

The scientific research carried out was performed both technically - tactically and postural unbalances, due to the fact that we intend to identify a possible relationship between the performance of the topspin attack and the posture of the body of the female juniors in table tennis. For the evaluation of the biomechanics and the execution speed of the topspin we used modern analysis software, *DartFish 360s*, meant to evaluate the angles between the arm-forearm in the 3 stages of performing a procedure and its necessary execution time (Fig. 1).

From the usage of the above mentioned computer software, there resulted the times required to perform the procedures expressed in hundredths of a second and the average values of the topspin attack performed with the forehand and the backhand, both from the no-spin ball and from the backspin ball.

We present the following values obtained (Tables 1 and 2): FHD (Forehand) Topspin from no-spin ball (resulting from blockage). The time required to execute the procedure expressed in hundredths of a second: 33.3 ;BHD (Backhand) Topspin from no-spin ball. The time required to execute the procedure expressed in hundredths of a second: 29.5 ; FHD. Topspin from spin

ball (backspin type). The time required to execute the procedure expressed in hundredths of a second: 48; BHD. Topspin from the spin ball. The time required to execute the procedure expressed in hundredths of a second: 38

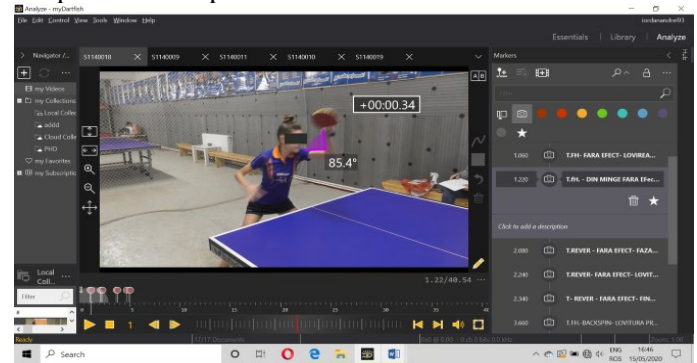


Figure 1. Image during the technical – tactical assessment processed by biomechanical analysis software, *DartFish 360s*, during the test with diagonal forehand topspin – the end of movement from blockage

The analysed feature	Average value
FHD. Topspin – Hit’s preparation <°	124.5
FHD. Topspin – Ball’s hitting <°	94.7
FHD. Topspin – The end of movement <°	74.3
FHD. Topspin – Time necessary for the execution in hundreds of a second	33.2
BHD. Topspin – Hit’s preparation <°	102.76
BHD. Topspin – Ball’s hitting <°	84.2
BHD. Topspin – The end of movement <°	129,75
BHD. Topspin - Time necessary for the execution in hundreds of a second	29,3

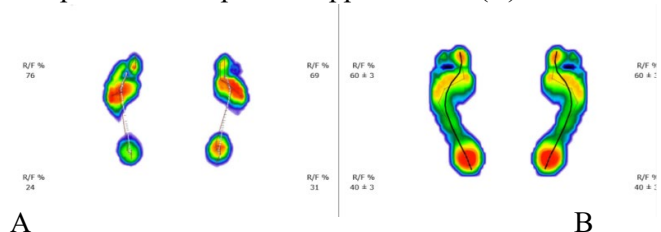
Table 1. The average of the values of the biomechanical indicators for forehand diagonal topspin from no-spin ball

The analysed feature	Average value
FHD. Topspin – Hit’s preparation <°	138,5
FHD. Topspin – Ball’s hitting <°	108,2
FHD. Topspin – The end of movement <°	75,9
FHD. Topspin – Time necessary for the execution in hundreds of a second	48
BHD. Topspin – Hit’s preparation <°	114,5
BHD. Topspin – Ball’s hitting <°	91,5
BHD. Topspin – The end of movement <°	137,6
BHD. Topspin - Time necessary for the execution in hundreds of a second	38

Table 2. The average of the values of the biomechanical indicators for forehand diagonal topspin from backspin ball.

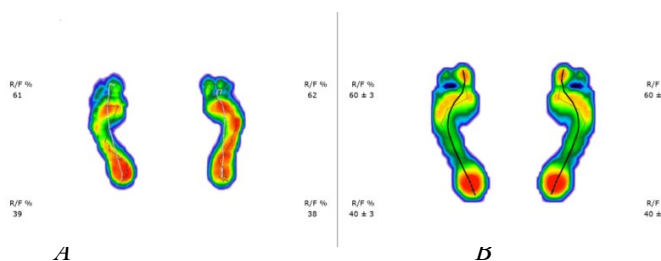
Following the technical – tactical, anthropometric, plantar pressures and postural unbalances assessments, there have resulted multiple values and correlations, all favouring an overview of the connections between them. Table 3 highlights the above.

The dynamic analysis of the female athlete's plantograms shows different ways of their movement, aspects that we want to highlight through the image represented by Figure 2, provided by the baropodometric device, which highlights the support mode of the assessed athlete (A) as compared to the optimal support mode. (B).



**Figure 2.** The value of the distribution of the plantar pressures versus the standard in the dynamic phase using the baropodometric platforms freeMed by Sensor Medica  
A = The percentage distribution of plantar pressures specific to table tennis in the case of the subject with the highest performance at the technical – tactical assessment.

B = The general value or the standard of an optimum distribution of the plantar pressures exercised in normal conditions.

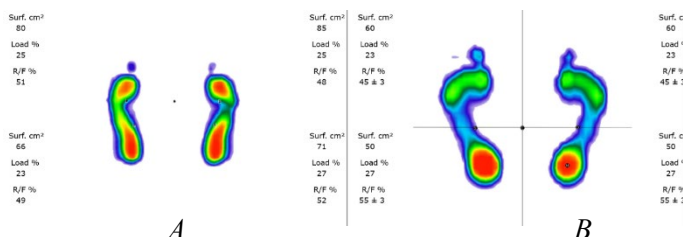


**Figure 3.** The value of the distribution of the plantar pressures of the subject vs. the general value in the dynamic phase using the baropodometric platforms freeMed by Sensor Medica

A = The percentage distribution of plantar pressures specific to table tennis in the case of the subject with the highest performance at the technical – tactical assessment.

B = The general value or the standard of an optimum distribution of the plantar pressures exercised in normal conditions.

\*From the dynamic assessment., a bilateral plane foot and a deficient way of movement as compared to the specificity of the table tennis (performed on the sole) are observed, with a negative influence at the level of the topspin attack, this comparison being achieved in relation to the other female athletes assessed, registering the lowest mean of the success.

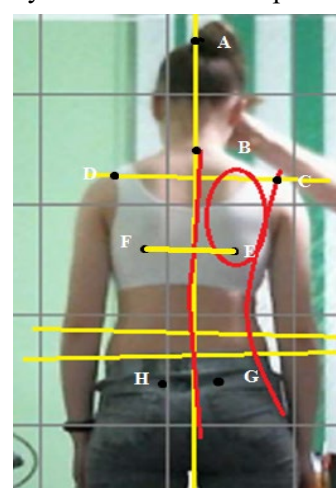


**Figure 4.** Distribution of the centre of gravity, as compared to the distribution of the centre of gravity in static phase result from using the baropodometric platforms freeMed by Sensor Medica

A = The Distribution of the centre of gravity specific to table tennis in the case of the female athletes assessed.

B = The Distribution of the centre of gravity or the standard.

In Figure 4. - A, and in the case of the other athletes assessed, a forward projection of the centre of gravity is observed, aspect resulting from the fundamental position specific to current table tennis, in which the trunk is inclined forward and the support is made on the forefoot, the trunk moving often from the inclined to the bent position in the dynamics of the game, especially in attack. According to the data taken from the postural analysis using the images, the somatoscopic examination shows a scoliotic attitude (lumbar sinister-convex and thoracic dextro-convex) in the case of the female juniors assessed, according to the observations in Fig. 5. We consider that these scoliotic deficiency result from the motor skills specific to table tennis and the lack of timely notification by the coach and the sports doctor of this deficiency,



**A** – Subject's vertex  
**B** – The prominence of C7 vertebra  
**C** – Right shoulder  
**D** – Left shoulder  
**E** – The tip of right scapula  
**F** – The tip of left scapula  
**G** – Prominence of postero-superior iliac spine R.  
**H** – Prominence of postero-superior iliac spine L.  
implicitly the lack of a postural improvement protocol.

**Figure 5.** – Image highlighting the scoliosis, resulting from the postural assessment of the junior female athlete resulting from using softwar FreeStep By Sensor Medica

**DISCUSSION**  
The aim of this study is to assess postural deficiencies and to assess the level of consolidation of the topspin attack, we can identify the correlations between them which would facilitate the creation in the future of an efficient postural improvement program.

The two findings were: all juniors' players have postural deficiencies and plantar imbalances, and a high weight of the athlete, she will have a flat leg and a low efficiency in the attack phase. And we consider that personalized plantar supports are very important in this age category and a recovery protocol through exercises performed asymmetrically, depending on the concavity of the spine.

From the statistical – mathematical analysis applied to the data obtained from the assessment, many strong correlations have resulted, as compared to the other specific levels (without correlation, poor correlation, moderate correlation and strong correlation). In the case of strong and moderate correlations at Test 1, the correlations related to the arrows of the lumbar spine ( $r = 1.00$ ) and ( $r = -0.99$ ) of the force of the palmar flexors were highlighted. In the first case we have a correlation directly proportional from which it results that a better technical – tactical success involves a higher value of the spine arrows in lumbar area (a highlighted lumbar curve), and at the second correlation we have an inverse ratio with the following significance: a success superior to the topspin attack involves a low force of the palmar flexors. In the case of strong and moderate correlations at Test 4, the correlations related to the thorax elasticity ( $r = 0.97$ ) and ( $r = -1.00$ ) of the bust have been highlighted. In the first case we have a directly proportional correlation from which it results that a better technical – tactical success involves a higher value of the thorax elasticity, and in the second correlation we have an inverse ratio with the following significance: a success superior to the topspin attack involves a lower value of the bust.

In the case of strong and moderate correlations at Test 5, the correlations related to Schober Test on flexion ( $r = 1.00$ ) and ( $r = -0.78$ ) the lateral mobility of the unhandy arm have been highlighted. In the first case we have a directly proportional correlations from which it results that a better technical-tactical success involves a higher value at Schober Test on flexion, and for the second correlation, we have an inverse ratio with the following significance: a success superior to the topspin attack involves a lower lateral mobility on the unhandy arm.

From the dynamic assessment of the female junior athlete (Fig. 2, variant A), it is observed a hollow (scooped) foot and a movement mode specific to table tennis, performed on the forefoot (sore) with beneficial implications at the level of the topspin attack (registering the best performance) as compared to the other athletes assessed.

## CONCLUSIONS

In the case of the means of the technical – tactical tests and the posture examination within the scientific research assessment, the following strong correlations have resulted, intended to guide the specialists for the optimization of the capacity and performance objectives. The strong correlation resulting from the technical – tactical assessment in relation to the weight ( $r = -0.78$ )

signifies a reverse proportionality, demonstrating the fact that a superior success in technical – tactical area involves a smaller weight of the female athletes. In the case of the strong correlation resulting from the technical – tactical assessment in relation to the waist ( $r = 0.64$ ) signifies a directly proportional ratio demonstrating the fact that a better success in the topspin attack involves a larger waist of the female athletes. The strong correlation resulting from the technical – tactical assessment in relation to the bust ( $r = -1.00$ ) signifies a reverse proportionality demonstrating the fact that a superior success in the technical –tactical area involves a smaller bust of the female athletes. The strong correlation resulting from the technical – tactical assessment in relation to the thorax elasticity ( $r = 0.96$ ) signifies a direct proportionality demonstrating the fact that a better success in the topspin attack involves a higher thorax elasticity of the female athletes. The strong correlation resulting from the technical – tactical assessment in relation to the plantar pressure of the left foot ( $r = 0.84$ ) signifies a direct proportionality demonstrating the fact that a higher pressure exercised on the sole left foot involves a superior success in the technical – tactical tests (at the hit with forehand in the case of right-handed female players).

The lateral mobility of the spine is much higher on the unhandy arm side, being explained by the fact that in the adopted play tactic, both in female and male players, the positioning, initiation and finalization of the forehand attack predominate, reason for which the flexion of the trunk in the side of the handy part causes a muscular – articular elongation higher on the diametrically opposite side (unhandy arm).

From technical – tactical point of view, the results obtained with the help of the biomechanical analysis software highlight a difference between the execution time of the topspin with forehand and with the backhand from backspin ball, as compared to the no-spin ball resulted from the blockage. The times necessary for the execution of the procedures in the case of backspin balls are higher due to the spin of the ball, aspect involving a larger span of the execution angles and trunk twists (e.g.: topspin with forehand from backspin ball, *0.48 seconds*, as compared to topspin with forehand from no-spin ball *0.33 seconds*). The angle value between the arm and forearm for the execution of topspin forehand procedure on the preparatory part of the hit, in the case of backspin balls are higher (e.g.: 138.5 from spin ball vs. 124.5 from no-spin ball), due to the spin of the ball, aspect which involves a larger span of the execution and trunk twist angles (e.g.: from backspin ball, *0.38 seconds*, as compared to no-spin ball, *0.29 seconds*).

A good processing of the main muscle and articular groups involved, specific to the motor skills in table tennis, mainly oriented on the shoulder, trunk and lower



limbs area, will facilitate the optimization of the topspin attack by preventing and reducing accidents.

Also, the implementation of customised plantar supports will represent another means of optimization of the attack in female junior players.

For the continuation of this scientific research, we would like to involve in the future a greater number of subjects (approximately 20 female junior players) for a picture at macro level on the topspin attack and the problems generated by it at the level of body posture. From the accumulated experience and data collected from the above mentioned scientific research, we would like to create an assessment system and an efficient amelioration program achieved with the help of the actual methods and means in order to optimise the performance capacity and to improve the life quality in female junior players in table tennis.

#### **Declaration of conflict of interests**

There is no conflict of interest for any of the authors regarding this paper.

#### **Informed consent**

Parental consent was obtained for each child after explaining the nature of the assessments, while ensuring that they were strictly anonymous and confidential. They were informed that they had the right to stop the experiment without prejudice. This study was conducted with the consent of the table tennis coaches.

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*Table 3. – Correlations between the (topspin) technical – tactical - anthropometric – plantar pressures and postural unbalances assessments*

NO.		S.	Correlations																				
			W.	WS.	B.	SP.	B.D.	T.E.	SHB.		D.-S.	LAT.		PAL. FLEX. FORCE		SPINE ARROWS		AREA (cm²) DYNAMIC ANALYSIS		P. P. (%) STATIC ANALYSIS		P. P. MAX. (gr/cm²)	
									FL.	EXT.		H.A.	U.A.	H.A.	U.A.	CVL.	LB.	L.	R.	L.	R.	L.	R.
1	BA	48	171	79.5	166	29	12	11	5.5	11	39	43	14.5	8	69	69	142	132	51	49	563	561	
2	PD	54.3	168	83.5	160	28.5	8	10.5	7	9	42.5	44	20	10	48	30	142	136	49	51	479	434	
3	PR	78.5	170	84.5	167	34	5	11	10	0	27	32	18	20	117	40	146	141	48	52	523	531	
4	GD	56	170	82.3	174	30	-4	10	9	2	25	27	30	20	23	23	134	143	43	57	544	543	
5	RD	54	165	80	168	32	3	3	6	4	32	34	25	30	45	34	154	143	56	44	476	425	
6	DS	52	160	76	160	32	10	6	4	6	43	41	10	20	45	89	134	123	49	51	476	486	
7	AB	34	152	80	157	26	5	4	6	0	43	35	25	10	45	65	134	135	52	48	500	400	
8	GL	47	169	78.5	165	25	10	10	5	4	35	40	13	10	45	45	135	142	49	51	400	503	
9	AD	75	172	86	168	33	3	12	6	3	24	27	20	20	100	50	150	155	52	48	540	545	
10	TF	45	165	76	159	28	10	6	6	8	35	40	5	10	56	65	165	160	49	51	512	532	
11	IG	65	160	73	170	27	7	12	5	0	27	30	20	25	15	20	131	145	51	49	563	521	
12	EV	70	169	81.5	159	28	6	12	9	0	30	35	25	30	34	54	145	135	48	52	476	432	
13	PA	76	172	U0	167	34	5	11	10	5	27	32	15	20	11	3	140	145	48	52	523	531	
CORREL T.1		-0.46	0.89	0.91	0.59	-0.20	0.78	0.69	-0.58	0.44	0.30	-0.15	-0.99	-0.42	0.02	1.00	0.53	-0.47	0.84	-0.84	0.99	0.99	
CORREL T.2		-1.00	0.05	0.82	0.40	0.95	0.93	0.28	-1.00	1.00	0.98	0.78	-0.39	-1.00	0.02	0.49	-0.47	-1.00	0.89	-0.89	0.64	0.61	
CORREL T.3		-0.86	0.51	0.99	0.07	0.69	0.99	0.21	-0.92	0.76	0.40	0.40	-0.78	-0.84	-0.51	0.84	-0.87	-0.87	1.00	-1.00	0.92	0.91	
CORREL T.4		-0.80	0.61	1.00	0.19	0.60	0.97	0.32	-0.87	0.78	0.68	0.29	-0.84	-0.77	-0.41	0.90	0.11	-0.81	0.99	-0.99	0.96	0.71	
CORREL T.5		0.32	0.94	0.33	0.99	0.57	0.08	1.00	0.19	0.34	0.67	-0.78	-0.78	0.36	0.73	0.70	0.31	0.31	0.19	-0.19	0.88	0.84	
CORREL M		-0.78	0.64	1.00	0.22	0.57	0.96	0.35	-0.85	0.76	0.46	0.58	-0.86	-0.75	-0.38	0.91	-0.64	-0.91	0.99	-0.99	0.75	0.55	

\*SP– Span; HA – Handy arm; UA – Unhandy arm; B - Bust; C – Correl; CVL – Cervical; S– Spine; BD - Biacromial Diameter; DS – Distance fingers – floor; R – Right; TE – Thorax elasticity; EX – Example; EXT – Extension; FL – Flexion; Fig. – Figure; FHD – Forehand; PAL FLEX. FORCE – Palmar flexor force; W - Weight; LAT - Laterality Test; LB – Lumbar; T.1-5 – Test 1-5; PP (%) – Plantar Pressure (load %); BHD – Backhand; S. ARROWS – Arrows of the spine; SHB - Schober Test; L – left; WS– Waist; TH-TC – Technical-tactic.

*Table 4. – Legend*

-0.25 < r < 0.25	Without correlation
-0.5 < r < -0.25 or 0.25 < r < 0.5	Poor correlation
-0.75 < r < -0.5 or 0.5 < r < 0.75	Moderate correlation
r < -0.75 or r > 0.75	Strong correlation



## Perspectives of Rehabilitation in Diabetic Neuropathy



WEB OF SCIENCE

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### Abstract

Diabetic Neuropathy (DN) is a complication that affects at least half of the patients with Diabetes Mellitus. Unlike other symptoms and signs that may sooner alarm the patients, DN manifestations tend to be rather silent, and so usually neglected by the patient for a long period of time, which can last for years. Therefore it's a “hidden complication of diabetes” label. Unfortunately, it is only when symptoms already affect the quality of life that the treatment becomes challenging when it comes to speaking of either etiological, symptomatic or rehabilitation strategies. Early diagnosis can also be tricky while aiming for lifestyle corrections and proper individualized treatment strategies. Rehabilitation methods for DN aim especially towards the improvement of articulation mobility and muscular strength amelioration, the suggested brief review of literature promoting this part of therapy essential for both prevention and amelioration of overall morbidity.

**Keywords:** *diabetic neuropathy, physical therapy, interdisciplinary approach, quality of life,*

### Introduction

Whereas there are many definitions and classifications for the concept of Diabetic Neuropathy (DN), we align to the ones that consider it a generic notion which includes different types of neuropathies, as neither one of them is present exclusively in Diabetes Mellitus (DM) (1). DN can manifest by either sensory, sensory-motor or autonomic polyneuropathies, as well mononeuropathies (carpal tunnel syndrome, cubital nerve neuropathy, peroneal neuropathy, cranial nerves III, IV, VI or VII affection) or different forms of radiculopathies and plexopathies (1,2).

Usual neuropathies have various manifestations such as numbness in the distal part of the limbs, unpleasant subjective sensations that are more evident at rest or during night time, as well as pain and discomfort along the anatomical tract of one or more peripheral nerves. It can also manifest as muscle pain, muscle loss, cramps, various non-specific autonomic or cranial nerves symptoms (3-5). Clinically, osteotendinous reflexes in the lower limbs can be diminished or absent, there can be signs of muscle atrophy, or even deformities of the feet (3,5).

Diagnosis is usually established clinically, however there are cases in which paraclinical testing can provide useful information the etiology, in case of doubt (asymmetrical or predominantly motor signs, rapid progressing disease or positive family history of neuropathy). In such situations, electromyography usually orientates the

differential diagnosis (1). Nevertheless, there are situations when the clinician must be well oriented and able to use whatever exploratory methods available. We recall the particular situation when one of our patients couldn't benefit from electromyographic testing due to technical issues, and underwent thermographic scanning of the lower limbs instead. Thermography, as an additional diagnosis tool, provided information related to the specific affection of neurons and vasa nervorum endothelium. Thermography could be combined with other image processing techniques, for instance using directional two-dimensional filters (6), (7), in order to detect and extract various relevant details from the analyzed images.

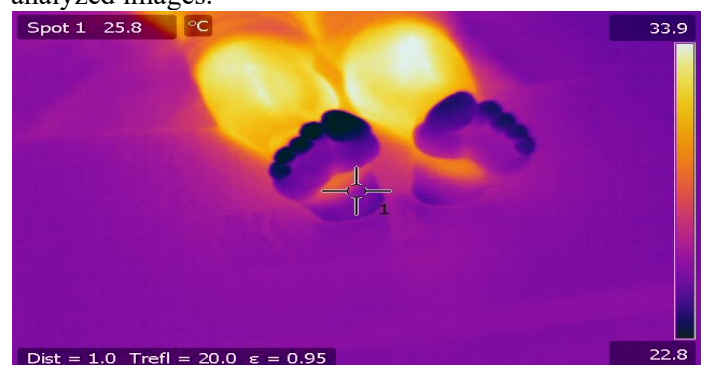


Fig. 1 Thermography: Specific thermal patterns in feet affected by diabetic neuropathy (yellow – normal temperature, tones of blue – metabolic and vascular affection)

Nowadays, the spectrum of diverse available diagnostic tools provide utility in postponing the progression of symptoms and signs, as the evolution of DN eventually leads to morbidity and negative impact on quality of life. This occurs especially by the development of diabetic foot, which requires interdisciplinary therapeutic approach, from a mixed team including diabetologist, neurologist and surgeon. Rehabilitation techniques emerge as necessary interventional treatments of ameliorating walking, pacing, overall muscle strength and improvement of mobility, for preventing or correcting further disability (and eventual potential progressive risk for amputations associated with the diabetic foot).

### **Aspects of clinical neurorehabilitation in Diabetic Neuropathy**

Neurorehabilitation techniques complete a therapeutic algorithm including nutritional support, long-term satisfactory glycemic control and efficient anti-diabetic treatment. The interdisciplinary approach to the patient with DN also includes a physical therapist, a podiatrist and masseur technician, as functional reeducation implies: electrotherapy, varieties of kinetotherapy (neuro-functional stimulation, proprioceptive neuromuscular facilitation, progressive resistance based active exercises), balneotherapy, sensory rehabilitation or tonifying massage (8).

Rehabilitation of DN applies to sensorial dysfunctions, motor impairment, autonomic neuropathy and ameliorating pain. The available body of data is suggestive for the benefits of physical therapy, and promotes rehabilitation techniques as necessary for completing both the pharmaceutical approach and the nutritional adjustments (9-11).

#### **a. Rehabilitation treatment for sensorial impairment**

A sensory deficit oriented treatment usually starts with pressure and pain training, aims towards improvements in differentiation between cold and warm stimuli and eventually deals with amelioration of stereognosis (8). Sensorial deficits usually take a long period to be corrected; nevertheless it is essential that correction should be recommended for preventing further morbidity. A recommended strategy is to deal with pain sensitivity first, followed by the tactile and the temperature recognition. These are the first actions to take for eventually regaining stereognosis (12, 13). Step by step, the patient will be able to recognize the correct site where the skin is touched by the examiner's tip of the finger, sensations of warm/cold, will perceive pain caused by a needle and will regain detection of vibrations (13,14).

Kinetotherapy techniques, both active and passive, provide opportunity for improving stereognosis. The patient will initially observe how the kinetherapist applies different stimuli, afterwards he will try to be aware of the sensations without visual contact, as part of the so called sensory rehabilitation exercises, which are recommended to last 5 or 10 minutes, and can be repeated several times during 24 hours (13-15).

Passive, postural and global rehabilitation programs may also benefit from the use of occupational therapy (15,16). On the other hand, the reorganization of sensitivity could occur with aberrations, such as perceiving a certain stimulus on a total different site than the one stimulated. In this situation, repetition of exercises will finally contribute to repairing the

correspondence between the excitation site and the cortical perception (13).

#### **b. Rehabilitation for motor functions**

Ameliorating muscle strength and improving joints motility, stance and gait, has a major utility in delaying the evolution towards articular rigidity, muscle atrophies, also with benefit upon vascular function (13, 15). A program designed for motor function will first assess passive mobilizations, up to 4 times a day. As soon as stability is overall improved, the active measures will aim an increase in muscle strength and resistance, with respect to the articular pain threshold and thus, progressively increasing the difficulty. When using stance exercises, the patient can be challenged to maintain balance in different situations, which will further improve the ankle stability (13, 15).

Therapeutic recommendations must always be adapted to the patient's cardiologic comorbidities (e.g. chronic miocardic ischaemia), associated respiratory and orthopedic pathologies, as well as the degree of sedentary lifestyle. Exercises can be adapted for increasing adaptability to effort and can include: walking, going up stairs or ramps, medicinal bike, swimming and occupational therapy (starting with daily household activities) (11-16). Promoting everyday lifestyle-based activities is an important fundament of compliance to the rehabilitation process. The most accessible cardio exercise is walking, especially that today pedometers and heart rate monitoring applications/ devices are neither expensive, nor by any means inaccessible. This way, both the patient and the physician can be involved in the diabetic patient's lifestyle optimization program (13, 17).

Exercises based on plantar flexion varieties have been proven to improve articular stability, muscle strength and ambulation (10). Dynamic or static stretching exercises, tai chi, and yoga, as well as swimming or aqua gym derived movements also help. Precautions must be taken in case of patients with plantar ulcerations, and all these techniques can only be practiced under supervision and coordination from recognized teachers/ technicians. This also mandatory for other types of exercises that may positively impact DN, such as ayurveda, qigong or wai tan kung (11).

Although exercises destined to increase effort tolerability are known to improve the distance of ambulation, they do not necessarily influence the velocity of walking; nevertheless overall results of physical therapy have a profound positive impact on the quality of life (18).

#### **c. Physical therapy in autonomic neuropathy**

Diabetic autonomic neuropathy can affect the quality of life through various cardiovascular, urological, sexual and ophthalmological manifestations, not to mention digestive or sudorimotor issues. Generally speaking, all of these benefit more or less from available drugs and by the means of interdisciplinary approach to the patient.

Physical exercise can positively influence the course of autonomic dysfunctions in DM. It can reduce dyslipidemia and the HbA1c value by increasing glycogen at muscular level, due to volume growth of muscle fibers. Practicing physical exercises impacts insuline resistance and regulates levels of ICAM-1, VCAM-1, E-selectine (adherence molecules, normally associated with endothelial dysfunction). There is also a favorable effect upon atherosclerosis (11).

Patients with DN are capable of improving their quality of life by walking, as there seems to be a connection between the intramuscular adipose tissue volume (IMAT) and the daily number of steps (19). Motor rehabilitation techniques also have a positive impact upon ventricular contraction, ameliorate oxygen diffusion by increasing the alveolar surface and increases oxygen extraction within tissues, as well as it influences fibrinolysis and coagulation processes (13). Orthostatism with eyes closed can be improved by moderate intensity cardio exercises (20). Physical exercises also improve reaction time, stance and gait, but not necessarily ameliorate the risk for falls (21).

For safety considerations of the physical exercises, parameters such as: frequency, intensity and type of exercise should be adapted to the patient's abilities, for better compliance during the so often long term rehabilitation process (11, 22). For all that, a well structured and individualized training program will have the intended results, unlike working predominantly on force or combined force-endurance exercises, which seem to have rather modest benefits (23).

#### d. Physical therapy as preventive care for diabetic foot ulcers

Ameliorating peripheral circulation reduces the risk for complications that might require surgical treatment and even amputations. For this matter, peripheral arteriopathy with associated progressing infection is an indicator for non-healing ulcer in the lower extremities (24). Sometimes the degree of affection is so important that the only solution left is amputation, followed by regaining mobility with an artificial limb. The peripheral arterial disease can be so evident in the foot, when irreversible, that changes of color (dark blue – tones of black) visible at thermographic scan could actually orientate the level for amputation.

On every possible occasion, the surgeon will first take into consideration the possibility of revascularization with minimum surgery trauma. This is the context in which endovascular procedures are considered to be the future standard in the treatment of diabetic peripheral arterial disease (25). Nevertheless, it is always easier to prevent that to treat. Peripheral arterial disease, beside general recommendations such as stopping smoking, correct glycemic control and antiplatelet treatment; also benefits from walking. Before any kind of physical indication, an effort test should be recommended for patients with history of cardiovascular disease (11).

Cardio exercises have the potential of improving endothelial functions, as observed with Doppler ultrasound. Muscle strength can be increased by neuroproprioceptive facilitation exercises and also training the healthy restant muscle fibers. Extension exercises aiming to correct the external rotation of the feet, as well as stretching maneuvers, passive movements for articular preservation and facilitation exercises for both proprio and exteroceptive perceptions, will result in prevention of muscle and tendon retractions and articular deformations (24).

Preventing foot ulcerations sometimes requires adequate shoes and devices, as well as educating the patient to examine and take care of his feet daily (11). This way the feet will be safe during exercises and normal everyday activities.

#### **Electrotherapy and other methods**

Neuropathic pain can be ameliorated by physical exercise, therefore improving the quality of life (26). Therapies based on low frequency currents add up especially to alleviating pain. One of the most known and used technique is the transcutaneous electric nervous stimulation (TENS). TENS act by presynaptic inhibition of the dorsal horn and direct inhibition of the abnormal excited nerve (8).

TENS is based on using surface electrodes that stimulate the painful area with high frequency and low intensity stimuli (aims A beta fibers, for 40-50 minutes, 50-100 Hz, impulses of 30-200 msec, intensity of 10-40 mA) or low frequency and high intensity stimuli (A delta, 1-5 Hz, 200-500 msec, 50-100 mA, for 30 minutes), either way, followed by a short term amelioration of pain. A intense variety of TENS is based on short term intense stimulation with currents of 100-150 Hz, 250-500 msec impulse, for 15-30 seconds. This effect lasts for 2 hours, by the stimulation of cutaneous A delta fibers and activation of inhibitory diffuse control of nociception (8), (27-29).

PENS (Percutaneous Electrical Nerve Stimulation) is TENS type technique that implies the use of needle electrodes, that will be placed in the painful dermatome (8).

Although there is some degree of pain amelioration, the physiological mechanisms implied are still not fully known. TENS is still an efficient method, useful at this moment, although without a set of parameters unanimously accepted, nor long term proof of efficacy (27-29).

High frequency current can be an alternative by HF/HTEMS/EMS (High Frequency External Muscle Stimulation, High-Tone External Muscle Stimulation and External Muscle Stimulation) and FREMS (Frequency-modulated Electromagnetic Neural Stimulation), still in debate, possible efficient, although more difficult to tolerate (27).

Results in pain treatment can also be obtained by using laser therapy with biostimulatory effect, vasodilatation, analgesic and anti-inflammatory effects, by foton absorption in the mitochondria resulting in an increase of the energetic capacity of the cell (8).

#### **Conclusions**

Prevention of further complications in DN is the key for avoiding a great deal of morbidity, especially related to the diabetic foot. Clinical exams should be completed with additional explorations, if necessary. Prevention of diabetic foot ulcers can benefit from a interdisciplinary view, in which the surgical approach, other than the decision of amputation, could play a more important part in the future. All these along with instruction of patients, maintaining a good glycemic control, nutritional advising and compliance to treatment, can benefit from adding rehabilitation algorithms, all aiming towards an improved overall quality of life.

Among these measures, physical exercise can be the fundament of a rehabilitation program which will combine cardio, resistance and flexibility strategies, individually adapted to the patient's needs. Electrotherapy shows promising results as well.

Further understanding of physiopathological mechanisms will surely provide better rehabilitation strategies for the following years.



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## Rehabilitation of patients with chronic rhinosinusitis after functional endoscopic sinus surgery



WEB OF SCIENCE

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### Abstract

**Introduction.** In the case of many patients with chronic rhinosinusitis (CRS), antibiotic and steroid therapies fail, and surgery is required. The recovery of patients after surgery equally depends on the postoperative behavior of each individual patient. The paper presents the outcomes of recovery after functional endoscopic sinus surgery (FESS) in a group of 74 patients.

**Methods.** The study was conducted in patients undergoing surgical treatment by FESS, performed by the same surgeon. For the development of the statistical database, the clinical records were collected by the same investigator.

**Results.** On the day of surgery and on the first postoperative day, 72.9% of patients reported facial pain, 41.8% nausea, 9.4% nasal bleeding, 8.8% vomiting. At 6 months postoperatively, 71.6% of patients estimated that they had a better quality of life than before surgery, 64.8% mentioned an improvement of olfaction as an effect, and 6.7% developed septal turbinate synechiae.

**Conclusions.** No major complications were identified in the recovery of CRS patients after FESS. Postoperative facial pain was less well tolerated by young patients (18-35 years old). The improvement of smell and the increase of disease-specific quality of life are the most relevant results of recovery after FESS mentioned by the patients included in our study. The otorhinolaryngologist and the family doctor play an important role in the education of patients regarding the importance of treatment with mineral and thermal waters in post-FESS recovery.

**Keywords:** *chronic rhinosinusitis, endoscopic sinus surgery, FESS, rehabilitation, ERAS protocols,*

### 1. Introduction

Chronic rhinosinusitis (CRS) represents a wide range of infectious-inflammatory processes affecting the nose and paranasal sinus mucosa simultaneously (1). CRS is an extremely common chronic disease, having a significant impact on the quality of life of patients. The pathophysiological mechanisms in CRS are varied, not mutually exclusive and are closely intricate, having the center in the microbial factor (2).

According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, CRS is diagnosed based on the following criteria: two or more symptoms (nasal blockage/ obstruction/ congestion or anterior/ posterior nasal discharge, ± facial pain/pressure, ± reduction or loss of smell) for ≥12 weeks, and endoscopic signs (nasal polyps, and/or mucopurulent discharge from the middle meatus and/or edema/mucosal obstruction in the middle meatus) and/or CT changes

(mucosal changes within the ostiomeatal complex and/or sinuses) (3).

The most simplified classification, based on pathogenesis, divides CRS into patients without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP) (4).

In CRS, the changes in the mucosa lead to favorable conditions for the growth and development of a microbial biofilm. Once formed, the biofilm determines the continuous presentation of antigens and maintains the chronic inflammatory process (5). At this stage, antibiotic and steroid therapies fail, and surgery is required.

Functional endoscopic sinus surgery (FESS) is the gold standard for treating CRS but is also used in rhinosinus tumor pathology (6-7). The goals of FESS in the treatment of CRS are enlarging sinus ostia, restoring physiological aeration of sinuses, improving mucociliary transport, and providing a better way for topical therapies

(6). Compared to the transoral approach, FESS is less invasive, allows the preservation of sinus anatomy and a reduction of the recovery time, with symptomatic improvements reported by approximately 90% of patients (8-9). Nevertheless, the surgical outcome not only depends on a successful surgical technique, but also on the postoperative behavior of patients and their compliance with the medical indications after surgery. The recovery of CRS patients after FESS can be delayed by the occurrence of the following situations: side effects/immediate postoperative complications (pain, hemorrhage, and crusting), short-term complications (infection, synechiae formation, and turbinate lateralization), and long-term complications (ostial stenosis, refractory disease, and disease recurrence) (9). The aim of this study is to present the results obtained by our team regarding the rehabilitation of CRS patients after FESS, in a group of patients undergoing surgery in the 2nd Otorhinolaryngology Clinic in Cluj-Napoca.

## **2 Material and method**

### **2.1 Study design and population**

We conducted a retrospective observational study on patients with CRS admitted to the 2<sup>nd</sup> Otorhinolaryngology Clinic of the University Clinical Hospital of Railway Company, Cluj-Napoca, in the period January 2017 - December 2019.

The patients were identified in the hospital database based on their CRS code at discharge. We included in the study patients diagnosed with CRS according to the EPOS 2020 criteria (3), with failure of conservative treatment and undergoing surgical FESS treatment in our clinic. We excluded patients under the age of 18 years, patients with previous rhinosinus surgery, psychiatric disorders, malignant tumors/associated autoimmune diseases, cystic fibrosis, Kartagener syndrome and granulomatous diseases, pregnant women, as well as those with incompletely recorded data.

For the development of the statistical database, the clinical records were collected by the same investigator. From each medical record, the following were extracted: age, sex, diagnoses, operative protocol, postoperative clinical evolution, treatment performed, result of rhinological examination at discharge, recovery evaluations. The patients' privacy and confidentiality were protected while respecting the laws in force: Law 95/2006 on Health Reform, art. 40 and art. 653, L. 95/2006, par. 2-4, the Medical Deontology Code, art. 16-20, as well as Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/CE (General Regulation on data protection, art. 12-20).

The study protocol was approved by the University Clinical Hospital of Railway Company Ethics Council under No. 10/09.12.2020.

### **2.2 Perioperative procedures**

Preoperatively, the patients were informed and counseled regarding the surgery and its potential complications, antianxiety drugs were administered for improving sleeping quality on patients' request, and patients fasted for solids and fluids for 8 hours prior to surgery.

After the allergy test, a preventive antibiotic (1 g ceftriaxone i.v.) was administered 30 minutes before surgery. After induction of general anesthesia through orotracheal intubation, the nasal vestibule was cleaned with iodine, the nasal cavity with saline solution, and a local vasoconstrictor agent was instilled prior to surgery. For all patients included in the study, FESS surgery (Fig. 1) was performed by the same surgeon (main surgeon). At the end of the surgery, metoclopramide was administered i.v. and anterior nasal packing with gauze or expandable Merocel nasal tampon was performed.

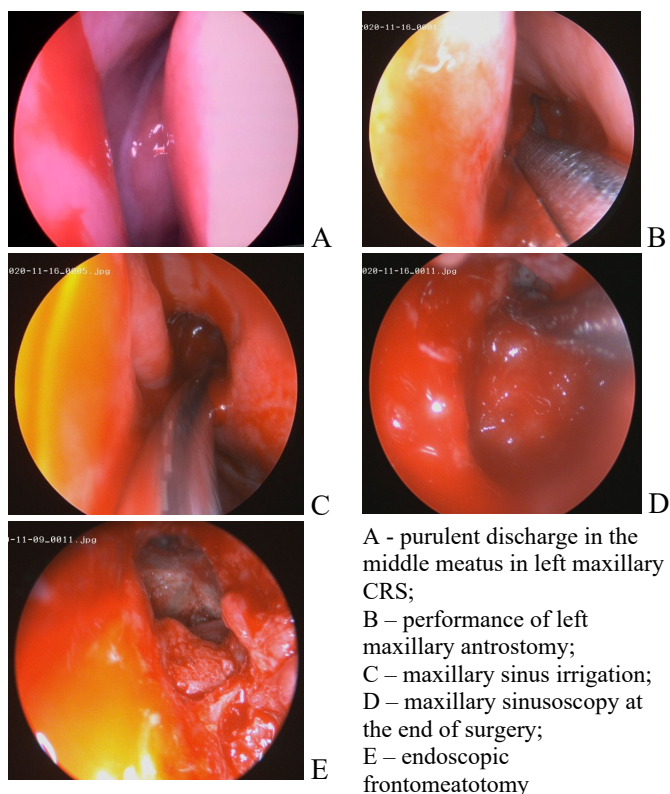
Postoperatively, patients benefited from bed rest, with guided mobilization on their request, electrocardiograph and blood pressure monitoring if needed, 8-hour fasting for solids and fluids. During the first 3 postoperative days, the treatment scheme included: ceftriaxone 2 g/day i.v. divided q12h, metamizole 2 g/day i.m. divided q12h (or in NaCl infusion 0.9%) (replaced by acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) in the case of patients allergic to metamizole), hemostatic cocktail (phytomenadione 20 mg/day, carbazochrome 3 mg/day, and etamsylate 500 mg/day, all divided q12h) in i.v. infusion of 500 ml NaCl 0.9%, and treatment of associated chronic diseases. The nasal packing was removed at 24 hours postoperatively, and for patients with moderate/severe intraoperative hemorrhage at 48 hours postoperatively.

The patients were discharged on the second postoperative day, except for elderly patients, with multiple comorbidities, who were discharged on the fourth postoperative day. At discharge, patients received the recommendation to use hypertonic seawater for nasal irrigation for 14 days, and then topical vitamin A oils for another 14 days.

### **2.3 Recovery evaluation**

Recovery evaluation was performed by the main surgeon at one month and 6 months after FESS. The patients were asked about their quality of life, facial pain, nasal bleeding and improvement of smell. Nasal endoscopy was performed for evaluation of nasal blockage, appearance of the mucosa, signs of infection, presence of crusting or synechia.





**Fig. 1.** Functional endoscopic sinus surgery – intraoperative aspects:

### 3 Results

The study inclusion criteria were met by 74 CRS patients, who gave their informed consent for participation in the study. Of all participants, 35 were male and 39 were female, aged between 18 and 84 years at the time of surgery. Odontogenic CRS was most common (39.2%,  $n = 29/74$ ), followed by CRSwNP (35.1%,  $n = 26/74$ ), CRSsNP (19%,  $n = 14/74$ ) and sphenoid CRS (6.7%,  $n=5/74$ ). The distribution of the CRS patient group depending on age, sex and diagnosis is shown in Table I.

**Table I. Distribution of the CRS patient group**

#### GENDER DISTRIBUTION

Gender	Male	Female	
No. of	35	39	74 patients

#### AGE DISTRIBUTION

Age	No	CRSsNP (Primary CRS diffuse non-type 2)	CRSwNP (Primary CRS diffuse type 2)	Odonto- genic CRS (Secondar y CRS unilateral)	Sphe- noid CRS
18-29	11	2	4	5	-
30-49	32	7	14	11	-
50-69	21	3	6	9	3
>70	10	2	2	4	2

Essential hypertension was found in 32.4% ( $n = 24/74$ ) of patients, and 14.8% ( $n = 11/74$ ) of patients had type 2 diabetes mellitus.

#### 3.1 Postoperative facial pain

This was the most frequent symptom reported by patients on the day of surgery and on the first postoperative day - 72.9% ( $n = 54/74$ ). Also, on the day of surgery and on the first postoperative day, an additional dose of analgesic was requested by 47.2% ( $n = 35/74$ ) of the patients and two additional doses by 18.9% ( $n = 14/74$ , of which 57.1%,  $n = 8/14$  were young patients aged between 18-35 years) - Table II.

#### 3.2 Postoperative nasal bleeding

On the day of surgery and on the first postoperative day, 9.4% ( $n = 7/74$ ) of patients complained of nasal bleeding that did not stop spontaneously, with a duration longer than 5 minutes. Each patient was administered an additional dose of hemostatic agent. Another nasal packing was required for 2.7% of all patients ( $n = 2/74$ , both of which had blood pressure increases over 160/90 mmHg at the time of hemorrhage; an angiotensin converting enzyme inhibitor tablet was administered sublingually, followed by a decrease in blood pressure values).

#### 3.3 Postoperative nausea and vomiting

Nausea was the second most frequent symptom reported on the day of surgery and on the first postoperative day - 41.8% ( $n = 31/74$ ), while vomiting represented 8.8% ( $n = 12/74$ ). Patients who complained of intense nausea and imminent emesis received metoclopramide 10 mg i.v. in slow infusion or i.m.

Other postoperative complications were dizziness (25.6%,  $n = 19/74$ ) and hypotension ( $<100/70$  mmHg, 10.8%,  $n = 8/74$ ).

#### 3.4 Recovery evaluation

At one month postoperatively, 41.8% of patients ( $n = 31/74$ ) estimated that they had an improved quality of life and were satisfied with the results of surgery; after 6 months, their proportion increased to 71.6% ( $n = 53/74$ ).

At one month postoperatively, 10.8% of patients ( $n = 8/74$ ) reported facial pain, and after six months, their percentage decreased to 4% ( $n = 3/74$ ).

Nasal bleeding was reported by 2.7% of patients ( $n = 2/74$ ) after one month postoperatively, and after six months, by no patient.

An improvement of smell (subjective) was reported by 31% of patients ( $n = 23/74$ ) at one month postoperatively, and after six months, their proportion increased to 64.8% ( $n = 48/74$ ).

At one month postoperatively, we identified the presence of crusting in 64.8% of patients ( $n = 48/74$ ), and after six



months, only in 2.7% (n = 2/74). At six months postoperatively, 6.7% (n = 7/74) of patients developed septal turbinate synechiae, and 2.7% (n = 2/74) had refractory CRS (Table II).

#### 4 Discussions

The recovery of CRS patients after FESS is influenced by perioperative procedures, the occurrence of postoperative complications, patient's perioperative stress, and particular individual factors (10-11).

**Table II. Recovery variables in CRS patients**

	Day of surgery and first postoperative day	One month postoperatively	Six months postoperatively
Facial pain	72.9% (n = 54/74)	10.8% (n = 8/74)	4% (n = 3/74)
Nasal bleeding	9.4% (n = 3/74)	2.7% (n = 2/74)	-
Nausea	41.8% (n = 31/74)	-	-
Vomiting	8.8% (n = 12/74)	-	-
Improvement of smell (subjective)	-	31% (n = 23/74)	64.8% (n = 48/74)
Crusting	-	64.8% (n = 48/74)	2.7% (n = 2/74)
Septal turbinate synechia	-	-	2.7% (n = 2/74)

#### 4.1 Enhanced recovery after surgery (ERAS) protocols

ERAS indicate a series of perioperative treatments aimed at accelerating recovery by reducing physical and mental stress associated with surgery, without increasing postoperative complications (12). Using ERAS protocols can improve the experience of hospitalization and quality of life, while the duration and expenses of hospitalization can be reduced. ERAS protocols are structured in three phases of care and contain both identical stages and stages that are newly introduced or applied differently than traditional protocols. ERAS protocols have been recently introduced in otorhinolaryngology as well, but there are few reports of ERAS in patients undergoing FESS (10,13). We present an ERAS protocol synthesis in patients undergoing FESS.

*Preoperative care* includes preoperative counseling for each patient, antianxiety drugs administered for improving sleeping quality as needed, a NSAID administered the night before surgery to induce preventive analgesia, and fasting 8 hours before surgery

for solids and 2 hours for fluids, with administration of a carbohydrate drink 2 hours prior to surgery (10).

*Intraoperative care.* A preventive antibiotic is administered 30 minutes before surgery, short-acting sedatives and short-acting opioid analgesics are administered during surgery, topical tetracaine and local lidocaine infiltration before surgery, crystalloid solutions are reduced when moderate colloid fluid is given, degradable hemostatic material for nasal packing is used (10).

*Postoperative care* includes bed rest, electrocardiograph monitoring, oxygen inhalation therapy for 2 hours, pain management, the possibility of feeding soft foods 2 hours after surgery according to gastrointestinal tract tolerance, out-of-bed activities guided according to individual recovery conditions. Long-term fasting, postoperative pain and lesions associated with FESS can aggravate the stress reaction, with the impairment of postoperative recovery (10).

#### 4.2 Postoperative pain management

Postoperative pain control is an important objective with an impact on patient's life and recovery. In a prospective study, 101 FESS patients were examined on the first postoperative day, after removal of the nasal packing, within a project of standardized evaluation of pain parameters. Statistical analysis showed that pain during the first postoperative day after FESS was moderate, young patients reporting higher scores than elderly patients (14). In our study, 57% (n = 8/14) of the patients who requested additional doses of analgesics on the day of surgery and on the first postoperative day were young persons aged between 18-35 years.

A survey conducted in 2018 among 168 members of the American Rhinologic Society representing all regions of the United States showed that the most commonly prescribed medications for pain after FESS were *opioid* pills (15). Another study regarding the responsible prescription of postoperative pain medications in the current context of opioid epidemic in the United States shows that the majority of patients undergoing FESS take approximately 5 opioid tablets after surgery, but concurrent septoplasty, younger age and a history of antidepressant use were associated with increased opioid usage (16-17). Some authors consider that the majority of patients would not need any opioid medication for postoperative pain control (18). There is evidence supporting the use of *NSAIDs*, *gabapentin*, *acetaminophen*, *α-agonists*, and *local anesthetics* can be viable options for the control of pain after FESS (19).

Unlike traditional postoperative analgesia protocols, according to which analgesics are administered when needed, ERAS protocols recommend preventive NSAID analgesia due to its efficacy and the low rate of adverse reactions. A NSAID (intravenous injection) for

preventive analgesia can be administered at 2 hours and 12 hours postoperatively (10).

#### 4.3 Postoperative nasal bleeding

It is a frequent complication after FESS. This is why at the end of surgery, anterior nasal packing with different, usually non-absorbable, materials is performed. Absorbable nasal packing was introduced more recently. Although there is some evidence in the literature that absorbable nasal packing would provide better results compared to nonabsorbable packing after FESS regarding postoperative nasal bleeding and synechiae, the lack of homogeneity between studies makes it difficult to draw definitive conclusions (20).

#### 4.4 Postoperative nausea and vomiting

Postoperative nausea and vomiting are among the most common adverse events following surgery under general anesthesia. The bilateral endoscopic injection of *lidocaine with epinephrine* in the sphenopalatine ganglion at the end of FESS is safe, non-invasive, and can reduce early postoperative nausea and vomiting (21). The placement of *pharyngeal packs* during FESS does not significantly improve postoperative nausea and vomiting and increases the risk of complications (including aspiration and death) (22).

#### 4.5 Olfaction recovery

Olfactory dysfunction, a common symptom in CRS patients, is caused by obstruction from polyps, nasal discharge, mucosal edema, and inflammation of the olfactory epithelium (23).

FESS improves the recovery of olfaction in CRS patients, especially if the patient had CRS with polyps, anosmia, and had no prior surgery. A deterioration of smell after FESS is rare (24-25). Preoperative systemic corticosteroid therapy ensures a better predictive rate of olfactory recovery after FESS, especially for CRS with polyps (26). Also, crenotherapy can improve olfactory function (27).

#### 4.6 Topical agents for nasal mucosa recovery

A number of topical agents for cleansing the nasal cavity and regenerating the sinonasal mucosa postoperatively have been studied.

Cleansing the nasal cavity by nasal irrigation plays an important role in postoperative care: it facilitates maintaining the permeability of the nasal fossae, reduces the amount of nasal secretions, inhibits crusting and accelerates the healing of nasal mucosal lesions. Unlike isotonic saline solution, *seawater* contains fewer sodium ions, but is rich in bicarbonates, potassium, calcium and magnesium. Bicarbonates reduce secretion viscosity, potassium and magnesium promote healing through limiting local inflammation, alkaline pH and elevated

calcium concentration optimize ciliary motility. Large-volume low-pressure nasal irrigation using undiluted seawater seems the most effective alternative for postoperative cleansing of the nasal cavity (28).

Regarding the use of hypertonic saline solutions/hypertonic seawater, there is no consensus in the literature. Some authors maintain that hypertonic saline can be associated with a greater benefit on endoscopic scores and mucociliary clearance than isotonic solutions and recommend it in postoperative care, especially for CRSwNP patients (29-30). A study shows that buffered hypertonic seawater has a better inhibitory effect on mucosal edema and crusting during the early postoperative care period of CRSwNP patients (31). Other authors argue that hypertonic saline solutions/hypertonic seawater can damage sinonasal epithelial cells in air-liquid interface cultures, inducing significant disruption of the epithelial mucociliary and barrier function, while isotonic saline/isotonic seawater does not affect epithelial mucociliary and barrier function (32). A meta-analysis on nasal irrigation with hypertonic saline solutions versus isotonic saline shows that hypertonic saline improves symptoms over isotonic saline in treating sinonasal diseases, but hypertonic saline causes more minor side effects than isotonic saline (33).

*Hyaluronic acid* and *steroids* are considered efficient factors in recovery management after FESS in CRS patients (34-36). Steroid-impregnated nasal packing and topical corticosteroid sinus irrigations have positive postsurgical effects on the recovery of CRS patients, especially those with polyps, undergoing FESS (37-38).

*Oily vitamin A and E solutions* stimulate nasal mucosal regeneration, prevent crusting and contribute to the restoration of epithelial barrier function (39). Topical treatment with  $\alpha$ -tocopherol acetate in elderly patients affected by CRS after FESS improves and speeds up the process of restoring the sinonasal mucosa (40). Vitamin A, alone or in combinations, prevents the formation of stenosis and is favorable for wound healing (41).

After healing of open mucosal lesions, *sun and sea therapy* can be an adjuvant in recovery. In addition to the chemical properties of seawater, marine flora can have an immunomodulatory therapeutic effect on sinusitis (42).

*Topical anti-infective solutions* can be considered as a potential option for refractory CRS patients with failed FESS (43). CRS patients showing recurrence after FESS despite postoperative irrigations with topical corticosteroids may respond to the addition of azithromycin as part of therapy (44).





A



B



C



D

**Fig. 2.** Romanian spa resorts with mineral and thermal waters useful for the recovery of CRS patients after FESS [55]: A - Slănic Moldova; B - Călimănești-Căciulata; C - Herculane; D – Olănești,

*Mineral and thermal waters* are recognized in balneology for their efficacy in postoperative recovery. Treatments with sulphurous, arsenical-ferruginous or chloride-sodium water may complete the rehabilitation program after FESS, leading to an improvement in nasal flow and a decrease in nasal resistance, a reduction of the mucociliary transport time and pathological microbial flora (45-46). Mineral treatments are administered by various respiratory therapy equipments (aerosols, inhalation, baric chamber) or by nasal irrigations (47).

In Romania, mineral and thermal waters in the resorts Govora, Slănic Moldova, Herculane, Călimănești-Căciulata and Olănești (Fig. 2) can be used during the recovery period of CRS patients (48). All patients included in our study received the recommendation of treatment with mineral and thermal waters during post-FESS recovery, but none of them followed this recommendation in the evaluation period for this study.

#### 4.7 Middle turbinate lateralization and synechia

The lateralization of the middle turbinate after FESS can obstruct the ethmoid and maxillary sinuses. Middle turbinate-septal suture medialization can be an effective method for preventing the lateralization of the middle turbinate and does not impair olfactory function (49-50). The prevalence of synechia seems to be lower (4.6-8%) when absorbable nasal packing is used compared to nonabsorbable packing (8-35.7%) (51). On the examination performed 6 months after FESS, synechiae were observed in 6.7% of the patients, using nonabsorbable packing for all patients.

#### 4.8 Recovery of elderly patients

Advanced age has been associated with functional changes in the sinonasal tract and alterations of local innate immune defense mechanisms (52). Furthermore, immunosenescence may have a negative impact on chronic inflammatory diseases (53). Thus, advanced age influences CRS pathophysiology and the response to medical and surgical therapy.

Elderly patients with CRS have higher rates of complications following FESS, and can present adverse effects related to steroid use, given the comorbidities associated with age. Data suggest that approximately one-third of patients over 60 years of age fail to achieve a clinically meaningful difference in disease-specific quality of life after FESS (54). We identified no significant difference between age groups regarding disease-specific quality of life after FESS.

#### 5 Conclusions

The patients included in our study reported no major complications in the first 6 months of the post-FESS recovery period.

Postoperative facial pain was less well tolerated by young patients (18-35 years old), in the case of which postoperative pain management may require higher doses of analgesics.

Improving olfaction and disease-specific quality of life is the main objective of recovery.

Because patients neglect treatment with mineral and thermal waters in post-FESS recovery, the otorhinolaryngologist and the family doctor play an important role in educating patients to understand the therapeutic benefits of this option.

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## Substantiation of the additional prescription of magnetotherapy in the complex of rehabilitation of children with concomitant diseases of the nervous system during remission of cancer



WEB OF SCIENCE

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### Abstract

**Introduction.** The increase in the number of children with oncological diseases requires development of effective methods of medical rehabilitation. **Purpose:** To determine the effectiveness of the use of low-frequency magnetotherapy (LFMT) in children with diseases of the nervous system, manifested in the period of remission of oncological diseases (OD) in the complex of sanatorium rehabilitation (SRR). **Methods:** Children with OD at the stage of rehabilitation in a sanatorium underwent a clinical examination: medical history, concomitant pathology, complaints, clinical examination, assessment of neurological status; instrumental studies: electroencephalography (EEG) - assessment of the bioelectrical activity of the brain; echoencephalography (EchoEG) - assessment of CSF dynamics; Doppler ultrasound (USDG) - assessment of cerebral circulation. For 25 children with concomitant diseases of the nervous system during the period of OD remission (17 people) and solid tumors (8 people), in addition to the general complex of SRR, magnetotherapy was prescribed for the cervical-collar zone according to the following method: magnetic induction 20 - 30 mT, exposure 10 - 15 minutes, every other day, for a course of 5 procedures. **Results:** The use of the therapeutic complex TFR with the additional prescription of magnetotherapy can reliably reduce children's complaints in remission of the OD for the impaired activity of the nervous system. According to the USDG indicators, statistically significant positive changes in cerebral hemodynamics were established. The results of ultrasound echoEG indicate the improvement of CSF dynamics. According to the EEG data, positive changes in the state of brain electrogenesis were established. **Conclusion:** The effectiveness of LFMT in children in the period of remission of oncohematological diseases with concomitant diseases of the nervous system has been substantiated.

**Keywords:** *children, oncological diseases, sanatorium rehabilitation, low-frequency magnetic therapy,*

### Introduction

Today, the rate of childhood morbidity with malignant neoplasms is steadily increasing in Ukraine and around the world (1, 2, 3). The problem is complicated by the fact that modern methods of treating the vast majority of malignant neoplasms in children have a damaging effect on normal tissues and structures of the body, including the central nervous system (CNS), which contributes to the development of side effects associated with dysregulatory pathology (4). Therefore, medical rehabilitation should be an obligatory part of modern antitumor treatment programs. One of the components of medical rehabilitation is physiotherapy - the use of various physical factors, among which low-frequency magnetic therapy (LFMT) should be mentioned. The therapeutic effect of magnetotherapy is based on the physiological effects of a static or alternating magnetic field: the appearance of weak electric currents in living

tissues, which alter the transmembrane potential of cells and the permeability of the cell membrane. The nervous, endocrine and cardiovascular systems are more susceptible to the influence of a low-frequency magnetic field. LFMT normalizes the autonomic functions of the body, reduces the increased vascular tone and, thus, has a certain hypotensive effect. Due to the increase in the oscillatory movements of the shaped elements, blood plasma proteins, blood circulation is activated in various organs and tissues, and trophic and regenerative processes are enhanced. Under the influence of LFMT, the formation of releasing factors of the hypothalamus and tropic hormones of the pituitary gland increases, which stimulates the function of the adrenal glands, thyroid gland, gonads, and other endocrine glands (5). The use of LFMT improves microcirculation, suppresses the inflammatory cellular response, increases the excitability threshold of pain receptors, reduces

muscle hypertonicity, and stimulates reparative processes (6). The authors have established the effectiveness of the use of LFMT to increase the speed of conduction of impulses along the nerve fibers, reduce perineural edema, increase the excitability of the central nervous system (CNS) (7, 8, 9). The data on the therapeutic effects of LFMT are given: vasodilator, anti-inflammatory, angioprotective, trophic, hypocoagulant, hypotensive, antispasmodic, etc. (10, 11, 12, 13). The above indicates the possibility of studying the effectiveness of magnetic therapy in the complex of sanatorium-resort rehabilitation (SRR) of children with concomitant diseases of the nervous system in the period of remission of oncological diseases.

**Purpose of the work:** to study the dynamics of clinical and clinical, and instrumental parameters in children with concomitant diseases of the nervous system in the period of remission of cancer with the additional appointment of low-frequency magnetotherapy.

#### **Materials and methods.**

The algorithm of examination of sick children at the stage of rehabilitation in a sanatorium State Institution "Specialized clinical sanatorium named after V.P. Chkalov" of the Ministry of Health of Ukraine, Odessa, included a general clinical examination (medical history, presence of concomitant pathology, complaints, clinical examination), assessment of neurological status; instrumental studies: electroencephalography (EEG) - evaluation of the bioelectrical activity of the brain; echoencephalography (EchoEG) - assessment of cerebrospinal fluid dynamics; Doppler ultrasound - assessment of cerebral circulation (14). The general complex of sanatorium-resort rehabilitation (SRR) for children with cancer (accompanied by parents) included:

- a gentle motor regime, climatotherapy, dietary nutrition; physiotherapy;
- singlet-oxygen cocktail,
- children's herbal tea (holosas with ascorbic acid),
- programs of psychological assistance to sick children and their parents.

Group 1 consisted of 25 children with concomitant diseases of the nervous system in the period of cancer remission - (17 people) and solid tumors (8 people) in the period of remission for more than 5 years, who were additionally prescribed magnetotherapy against the background of the

general SRR complex (they used the ALIMP- 1) on the cervical-collar zone according to the following method: magnetic induction 20 - 30 mT, exposure 10 - 15 minutes, every other day, for a course of 5 procedures. Group 2 consisted of 30 children with concomitant diseases of the nervous system in the period of cancer remission, received a general complex SRR without LFMT.

#### **Results and its discussion.**

Table 1 illustrates the positive dynamics of all complaints in children who received a medical complex with the additional use of magnetotherapy. These dynamics (weakness, fatigue, dizziness, intolerance to transport, and stuffiness) significantly exceeded the indicators in children prescribed a general complex of treatment.

According to the USDG indicators, statistically significant positive changes in cerebral hemodynamics in children of group 1 were established, which were accompanied by a decrease in the manifestations of cerebral angioedema, asymmetry of blood circulation and venous dyschemia, an increase in the circulatory reserve, and an improvement in the adaptive capabilities of the autoregulation apparatus and cerebral circulation (Table 2).

According to the indicators of ultrasound EchoEG of children of the 1st group, an improvement in CSF dynamics was revealed in the form of a statistically significant decrease of intracranial hypertension and the frequency of registration of additional echo signals (Table 3). It should also be emphasized that the hypertensive-CSF syndrome manifestations are halved, and the pulsation index decreases threefold.

In children of the 1st group, when analyzing the EEG, positive changes in the state of brain electrogenesis were found (Table 4). The state of electrogenesis was characterized by the normalization of the bioelectrical activity of the brain, accompanied by a statistically significant improvement in the functional activity of the cortex. This emphasizes the regulatory (optimizing) effect of LFMT on the functional state of the cerebral cortex. No significant changes in local pathology were revealed.

The immediate results of treatment of children in groups 1 and 2 are shown in Table 5. More positive changes were obtained in patients of group 1, which indicates the advantage of using LFMT.

The facts established by us are confirmed by other researchers, who cite data that using a magnetic field leads to a decrease in the side effects of radiation and chemotherapy of tumors. This is due to the protective effect of magnetic induction up to 30 mT from radiation; the influence of a magnetic field on the activity of immune reactions in cancer patients (15, 16). In clinical work, the effectiveness of the use of artificial magnetic fields in the rehabilitation of children with malignant tumors has been proven (17). This is since that artificial electromagnetic fields restore the normal rhythm of the activity of the of the central nervous system's regulatory centers, which contributes to the restoration of the activity of the integral central nervous system and, accordingly, the course of the vital processes of the organism.

### Conclusions.

1. The use of the medical complex SCR with the additional purpose of magnetic therapy can significantly reduce the children's complaint in remission with concomitant diseases of the nervous system.
2. Statistically significant positive changes in cerebral hemodynamics were found according to the indicators of ultrasound. Ultrasound results of EchoEG indicate an improvement in cerebrospinal fluid dynamics. According to EEG, positive changes in the state of electrogenesis of the brain. Thus, it can be considered justified to use low-frequency magnetic therapy in the sanatorium rehabilitation of children in the period of remission of cancer with concomitant pathology of the nervous system.

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Table 1. Dynamics of complaints in children of group 1 and Group 2, (M ± m)

Complaints	Group 1		Group 2	
	Before treatment	After treatment	Before treatment	After treatment
Weakness, fatigue	22(88,0±6,5)	6(24,0±8,5)*	26(86,7±6,2)	18(60,0±9,0)*●
Anxiety	10(40,0±9,8)	2(8,0±5,4)*	12(40,0±8,9)	6(20,0±7,3)
Mood lability, depression	11(44,0±9,9)	4(16,0±7,3)*	6(20,0±7,3)	4(13,3±6,2)
Poor appetite	7(28,0±9,0)	3(12,0±6,5)	8(26,7±8,0)	6(20,0±7,3)
Irritability	15(60,0±9,8)	5(20,0±8,0)*	18(60,0±8,9)	10(33,3±8,6)*
Sleep disorders	8(32,0±9,3)	1(4,0±3,9)*	10(33,3±8,6)	6(20,0±7,3)
Attention deficit disorder	15(60,0±9,8)	6(24,0±8,5)*	18(60,0±8,9)	10(33,3±8,6)*
Headaches	18(72,0±9,0)	8(32,0±9,3)*	21(70,0±8,4)	15(50,0±9,1)
Dizziness, intolerance of transport, shortness of breath	19(76,0±8,5)	6(24,0±8,5)*	22(73,3±8,0)	18(60,0±8,9)●
Feeling of a "lump" in the throat	12(48,0±9,9)	2(8,0±5,4)*	14(46,7±9,1)	8(26,7±8,1)
Cold and wet palms	7(28,0±9,0)	2(8,0±5,4)	8(26,7±8,1)	6(20,0±7,3)
Short-term pain in the heart	10(40,0±9,8)	4(16,0±7,3)	12(40,0±8,9)	8(26,7±8,1)
Tachycardia	5(20,0±8,0)	2(8,0±5,4)	6(20,0±7,3)	6(20,0±7,3)

Note. \* - p < 0.05 - the probability of the difference between the indicators before and after treatment;

● - p < 0.05 - the probability of the difference between the achieved indicators of the complexes after treatment

Table 2. Dynamics of indicators of ultrasound of the main vessels of the head and neck in children of group 1 and group 2

Indicators	Group 1		Group 2	
	Before treatment	After treatment	Before treatment	After treatment
Cerebral angiodystonia	17(68,0±9,3)	10(40,0±9,8)*	21(70,0±8,4)	15(50,0±9,1)
Decreased blood circulation	20(80,0±8,0)	10(40,0±9,8)*	24(80,0±7,3)	20(66,7±8,6)
Asymmetry of blood circulation	18(72,0±9,0)	10(40,0±9,8)*	22(73,3±8,1)	18(60,0±8,9)
Decreased adaptive capacity of the autoregulation apparatus	15(60,0±9,8)	8(32,0±9,3)*	18(60,0±8,9)	14(46,7±9,1)
Venous dysgemia,	22(88,0±6,5)	12(48,0±9,9)*	27(90,0±5,5)	20(66,7±8,6)*

Note. \* - p < 0,05 - probability of difference between indicators before and after treatment.

Table 3. Dynamics of ultrasound EchoEG in children of group 1 and Group 2, (M ± m)

Indicators	Group 1		Group 2	
	Before treatment	After treatment	Before treatment	After treatment
Phenomena of intracranial hypertension, %	22(88,0±6,5)	10(40,0±9,8)*	27(90,0±5,5)	20(66,7±8,6)*●
Hypertensive-CSF syndrome, %	10(40,0±9,8)	5(20,0±8,0)	12(40,0±8,9)	10(33,3±8,6)
Increasing the index of pulsations, %	6(24,0±8,5)	2(8,0±5,4)	7(23,3±7,7)	4(13,3±6,2)
Additional Echoes, %	8(32,0±9,3)	2(8,0±5,4)*	10(33,3±8,6)	10(33,3±8,6)●

Note. \* - p < 0.05 - the probability of the difference between the indicators before and after treatment;

● - p < 0.05 - the probability of the difference between the achieved indicators of the complexes after treatment

Table 4. Dynamics of EEG parameters in children of group 1 and Group 2, (M ± m)

Indicators	Group 1		Group 2	
	Before treatment	After treatment	Before treatment	After treatment
Changes in electrogenesis, %	15(60,0±9,8)	8(32,0±9,3)*	18(60,0±8,9)	16(53,3±9,1)
Changes in functional activity, %	15(60,0±9,8)	7(28,0±9,0)*	18(60,0±8,9)	14(46,7±9,1)●

Note. \* - p < 0.05 - the probability of the difference between the indicators before and after treatment;

● - p < 0.05 - the probability of the difference between the achieved indicators of the complexes after treatment

Table 5. Immediate results of treatment of children in groups 1 and 2, abs. number of patients, (G ± mg)%

Treatment results	Group 1			Group 2		
	Neurological syndrome			Neurological syndrome		
	vegetative-vascular, n= 8	asthenoneurotic n= 10	Cerebrovascular n= 7	vegetative-vascular, n= 10	asthenoneurotic n= 12	Cerebrovascular n= 8
Improvements	3 (37,5±17,1)	5 (50,0±15,8)	2 (28,6±17,1)	2 (20,0±12,6)	2 (16,7±10,8)	
Slight improvement	4 (50,0±17,7)	4 (40,0±15,5)	4 (57,1±18,7)	2 (20,0±12,6)	2 (16,7±10,8)	6 (75,0±15,3)
Unchanged	1 (12,5±11,7)	1 (10,0±9,5)	1 (14,3±13,2)	4 (40,0±15,6)	5 (41,6±14,2)	2 (25,0±15,3)
Deterioration				2 (20,0±12,6)	3 (25,0±12,5)	



WEB OF SCIENCE

## Applications of fitness function in Pubalgia affliction

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### Abstract

**Introduction.** The relationships among variables are important in medicine and sport, and the most common approaches use linear correlation for optimization and prediction. **Material and method.** We propose to o novel usage of a known method (the genetic programming algorithm) to construct a nonlinear model in a practical case for rehabilitation find out the mathematical formula for a relationship among many variables . This study seeks to find a mathematical function to estimate the current state of the patient: healthy, affected by Pubalgia. **Results and discussions.** In the proposed application, a mathematical relationship is sought for five variables that express a state of health for patients, plantar footprint, plantar footprint – right, plantar pressure, plantar pressure – right and the surface of the body weight center. **Conclusions.** In this article, genetic programming has been proposed to construct a mathematical function to estimate the patient's condition possibly affected by Pubalgia.

**Keywords:** *e-health, rehabilitation, genetic algorithm,fitness function,*

### Introduction

Linear regression and multiple linear regression (bivariate or multivariate) are used for modeling the relationship between variable (usually a scalar) and more explanatory variables (independent variables or correlated variables) in many areas of research and practical applications. The correlation used is linear that is the variables are testes if they are correlated linearly. If the correlation test has the value zero, this means that the variables are correlated linearly but no information is given about the possible nonlinear correlation. The nonlinear correlation is difficult to be discovered and the most common proposal is based on heuristics: the polynomial form or exponential form. If these approaches give no satisfactory results, no systematic method has been proposed in the medicine and sport and not only. There are studies that deal with relationship between or among variable but no mathematical formula is given in order for this relationship (1,2,3,4,5). The most common approach is the linear one, where a linear regression is used to discover the linear relationship, as in (5,6,7,8,9). Very few paper deal with nonlinear relationship in the area of medicine or/and sport, one of them is (10) , where a polynomial of degree two ( $y = a + bx + cx^2$ ) is proposed as nonlinear model

(along with a linear model,  $y = a + bx$ ) between anthropometric measures and the motor-endurance status. Recent paper suggests that nonlinear model are better but no practical example is given (10). Pubis osteitis is a non-infectious inflammation of pubic symphysis. It was first described in 1924 as a complication of surgical interventions performed above pubic symphysis, but it was later found that this condition also occurs as an inflammatory process in athletes causing pain in the insertion of abdominal muscles and at the level the pubic symphysis joint. The main symptoms experienced by athlete affected by the pubis osteitis are decreased joint mobility, pain in the inguinal region, exacerbated pain in running, stroke of the ball, directional change or even during routine activities such as car climbing, walking, climbing stairs or even in the position of orthostatism. A method to construct a mathematical function that can estimate the current state of the patient (practical an e-health index) based on experimental non-invasive measurement over patient is proposed.

The method use the genetic programming techniques and three qualitative levels of patients' affection by Pubalgia : healthy, affected by pubis osteitis or tendency towards normalization. The results were

with good results for experimental data and other improvements are in progress. Pubis osteitis is a non-infectious inflammation of pubic symphysis (12). It was first described in 1924 as a complication of surgical interventions performed above pubic symphysis, but it was later found that this condition also occurs as an inflammatory process in athletes causing pain in the insertion of abdominal muscles and at the level the pubic symphysis joint. The main symptoms experienced by athlete affected by the pubis osteitis are decreased joint mobility, pain in the inguinal region, exacerbated pain in running, stroke of the ball, directional change or even during routine activities such as car climbing, walking, climbing stairs or even in the position of orthostatism. Specialty studies have shown that the main causes that may cause puberty osteitis are:

- Sports activities (example: football, hockey, tennis);
- Minor repetitive trauma (specific to sports activities);
- Major trauma;
- Surgery (gynecological or urological);
- Rheumatologic disorders

A method to construct a mathematical function that can estimate the current state of the patient (practical an e-health index) based on experimental non-invasive measurements over patient is proposed. The method use the genetic programming techniques (13) and three qualitative levels of patients' affection by Pubalgia : healthy, affected by pubis osteitis (14,15,16,17) or tendency towards normalization. The results were with good results for experimental data and other improvements are in progress

### **Matherial and Methods**

The study was conducted on a number of 35 subjects, of which 30 healthy subjects and 5 affected by pubalgia (pubis osteitis) . All subjects had the weight between 60 and 90 kg, the size between 170 and 190 cm, the plantar size ranging from 22.5 to 28.5 cm and the age between 20 and 30 years. All 35 subjects were evaluated with a Pedro OEM / DF Postrotest, and at the end of the evaluation, plantar imprint, plantar pressure, and general weight center were collected. Anthropometric development assessment was used to select subjects, resulting in better control of variables.

We used:- An electronic scale "SilverCrest" model "SPWS 180 B2" manufactured on 12.2013. in order to measure the weight in the range of 60-90 kg;

- A Wunder marker for measuring the waist in the range 170-190 cm;

- Metric band (centimeter) with gradient from 1 cm to 150 cm. in order to measure the planting size in the range 22.5 - 28.5 cm.

Post-urology-stabilometry are new methods of investigation used both for establishing the clinical and differential diagnosis and for following the evolution of these disorders, being considered non-invasive methods. A posturotest with the operating system was used to perform the pilot research: OEM / DF PEDAN, DISP MED. CLASSE I "since 2007.

Subjects tested by posturotest were trained and informed as follows:

- on the next test;
- on board the platform;
- on the movements they can perform once they are on the posturotest (they must remain motionless until the therapist's signal and follow a point on the wall located perpendicular to the visual ray);
- on the equipment (shoe and barefoot);

Subjects affected by puberty (osteitis of the pubic), in number 5, received rehabilitative treatment (8). Rehabilitation treatment was lasting for 4 weeks (20 sessions), each session lasting 50-70 minutes and was composed of massage techniques, PNF techniques, stretching and therapeutic physical exercises.

The treatment session for each individual was structured as follows:

- Massage (smoothing and friction) - duration of 5-10 minutes;
- Stretching (passive) - duration 5-10 minutes;
- Massage (smoothing and friction) - duration of 5-10 minutes;
- Muscle proprioceptive neuromuscular facilitation (relaxing opposition and slow inversion with opposition) - duration 5-10 minutes;
- Massage (smoothing and friction) - 5-10 minutes,
- Stretching combination with proprioceptive neuromuscular facilitation techniques - 5-10 minutes duration,
- Massage (vibration) - duration of 5-10 minutes.

Dosage consisted in varying the duration of each technique used, depending on the individual's motor skills, stage, pain. This study seeks to find a mathematical function to estimate the current state of the patient: healthy, affected by Pubalgia or tendency towards normalization (treated). This function will be built on a number of five parameters

(Table 1), such as: plantar footprint – left (PFI), plantar footprint – right (PFR), plantar pressure - left (PPI), plantar pressure – right (PPR) and the surface of the body weight center (Sbwc). In Table 1, we can see some of the 30 healthy subjects used in the study, and in Table 2, we identify the values of the 5 subjects affected by Pubalgia. Following the physical therapy treatment (performed over a four week period, 20 sessions), the subjects were retested and the data obtained can be seen in Table 3. In order to find this math function, we used the data from Tables 1, 2 and 3, but at the same time we used the genetic programming that are an evolutionary algorithms and include a set of individual elements represented in the form of binary strings, the so called population, and a set of biological operators defined on the population.

**Table 1.** Example of values from the 30 healthy subjects.

Subject	PFR (%)	PFI (%)	PPR (kgf)	PPI (kgf)	Sbwc
1.	41.8	58.2	32	18.8	0.28
2.	48.2	51.8	42.4	35.5	0.408
3.	33.7	66.3	23.5	12.9	0.323
4.	42.9	57.1	23	21.5	0.206
5.	46.5	53.5	27.2	22.6	0.2
6.	38.6	61.4	19.6	17.7	0.135
7.	36.1	63.9	37.5	24.6	0.157
8.	39.3	60.7	26.7	22.8	0.107
9.	43	57	38.4	31.6	0.204
10.	44.5	55.5	16.5	16.1	0.261
11.	41.3	57.3	31.2	25.6	0.21
12.	47.2	51.6	41.3	18.2	0.306
13.	34.1	64.3	22.5	35.2	0.158
14.	45.6	56.9	22.3	12.4	0.108
15.	36.8	52.5	26.9	21.2	0.263
16.	37.9	60.4	19.2	22.5	0.3
17.	41.3	57.3	37.3	17.4	0.127
18.	39.8	54.5	15.9	30.3	0.137
19.	43.8	60.4	40.4	12.5	0.206
20.	37.6	59.7	23.7	27.3	0.246
21.	38.5	56.3	24.9	24.4	0.4
22.	41.6	64.9	31.8	31.3	0.156
23.	44.3	61.1	15.3	32.5	0.321
24.	39.8	57.8	27.8	19.8	0.236
25.	41.5	51.1	31.7	23.5	0.118
26.	39.7	53.7	28.3	29.6	0.298
27.	41.2	60.3	31.2	31.4	0.119
28.	34.3	61.8	19.7	27.5	0.207
29.	36.6	59.2	41.9	23.9	0.213
30.	43.9	56.4	42.3	21.1	0.112

**Legend:** PFR = plantar footprint – right, PFI = plantar footprint – left, PPR = plantar pressure – right, plantar PPI = plantar pressure - left, Sbwc = surface of the body weight center

**Table 2.** Values from the 5 subjects affected by pubalgia (pubis osteitis).

Subject	PFR (%)	PFI (%)	PPR (kgf)	PPI (kgf)	Sbwc
1.	63.8	34.2	56.3	13.8	0.145
2.	68.4	31.6	60.1	14.5	0.121
3.	62.1	37.9	70.6	25.6	0.171
4.	67.8	32.2	51.3	24.9	0.125
5.	67.7	22.3	65.6	31.4	0.116

**Legend:** PFR = plantar footprint – right, PFI = plantar footprint – left, PPR = plantar pressure – right, plantar PPI = plantar pressure - left, Sbwc = surface of the body weight center

**Table 3.** Values from the 5 subjects that performed a physical therapy treatment.

Subject	PFR (%)	PFI (%)	PPR (kgf)	PPI (kgf)	Sbwc
1.	60.8	39.2	50.3	20.8	0.17
2.	61.4	38.6	55.1	15.5	0.161
3.	58.1	38.9	66.6	26.6	0.211
4.	66.8	32.2	50.3	24.9	0.139
5.	62.7	24.3	61.6	32.4	0.126

**Legend:** PFR = plantar footprint – right, PFI = plantar footprint – left, PPR = plantar pressure – right, plantar PPI = plantar pressure - left, Sbwc = surface of the body weight center

The scope of the study is to find out a nonlinear relationship between the variables noted by PFR –  $x_1$ , PFI –  $x_2$ , PPR –  $x_3$ , PPI –  $x_4$  Sbwc –  $x_5$  and a health index  $I_h$  –  $y$ , structured on three levels, as  $y = g(x_1, x_2, x_3, x_4, x_5)$ . The target values, health index are confirmed by three independent physicians. In our case, the application of this method produced an accuracy of (12%), from complete set of values, a very poor result. This results show clearly that if we want to improve the accuracy of the model, a nonlinear solution is a feasible one. It is very hard to guess such formula and we chose a systematic method inspired by evolutionary algorithms, genetic programming.

Genetic programming use few new notations in addition with the known ones, used in Genetic programming. The terminals ( $T$ ) are the variables used for modeling the functions, in our case  $\{x_1, x_2, x_3, x_4, x_5\}$ . The nodes are usually mathematical functions (exponential, sinus, logarithmic, power, etc.) or symbols of operations, as sum, subtracts, multiplication.



## Results and Discussion

The genetic programming is an evolutionary method applied to a population of programs in order to achieve a predefined objective usually characterized by a fitness function (10).

The most common usage of fitness function is minimization of the objective function given by a fitness function. If the objective is maximization of the function  $x_{fitness}$ , simply we can consider the minimization of the function:  $y_{fitness} = -x_{fitness}$ , the squares errors as goal of the genetic programming method. In our case, the error is given by the difference between desired value to be obtained by  $\hat{y}$  function and the real value of  $y$  obtained by applying the formula of function. In genetic programming, the chromosomes are functions represented by trees in inverse Polish notation. The main steps in genetic programming algorithms are similar to evolutionary algorithms: selection, crossover and mutations. We must remark that all these genetic operators act on trees and sub-trees, different from other evolutionary algorithm where chromosomes are represented by linear sequence of genes. The main steps in genetic programming are described in what is following (11).

A first population of individuals is created using a random generator (usually uniform distribution). Each individual from population is evaluated according to fitness function. Using the fitness function, the selection operator selects the pairs of individuals (according to selection mechanism: roulette, tournament, stochastic sampling, etc.) in order to apply the crossover operator to create new individuals. The less performing individuals are discarded and the best individuals are grouped in a new generation. Mutations are performed in order to prevent the premature convergence and elitism disadvantages. The population is evaluated again and the loop continues until stop conditions are fulfilled. The stop condition can be a predefined number of iterations or a number of steps (three or four generation) that cannot produce an improvement of fitness for the best individual from population.

In our application we are looking for a function of type:

$$F_{x,y,z, steel} = g(a_p, f_z, v_c) = \sum_{k=1}^{N_g} b_k \cdot g_k(a_p, f_z, v_c). \quad (1)$$

In order to compute  $g_k$  and  $b_k$ ,  $k = \overline{1, n}$  ( $n$  is the maximum number of genes) we use a set of terminals and operators (2):

$$T = \{a_p, f_z, v_c, RA\}, \quad (2)$$

$$F = \{+, -, *, /, \exp, \text{power}\}. \quad (3)$$

In terminal set,  $RA$  is a random value in the range  $[-10.0, +10.0]$ . In the proposed application, a mathematical relationship is sought for five variables ( $x_1, x_2, x_3, x_4, x_5$ ) that express a state of health for patients  $Y$  (healthy = 0.1, treated = 0.5, affected = 0.9): plantar footprint – left (PFI), plantar footprint – right (PFR), plantar pressure - left (PPI), plantar pressure – right (PPR) and the surface of the body weight center (Sbwc).

There are few software tools that are used for genetic programming: GPLAB, GP dot NET, GPTIPS, GP-OLS and also specialized software tools (Poly LX, texture analysis for petrol). An interesting extension of genetic programming is the combination of more genes represented by trees in a linear fashion and optimization of individuals in two stages: optimization of each gene and optimization of the linear combination (linear regression) (13). The optimal weights in linear model are obtained by ordinary least squares to regress the genes versus the output data (13).

In our application, we used the software *GPTIS* (10). Practically, the nonlinear model is modelled by a pseudo-linear model with nonlinear genes. A common measure of the degree of appreciation of a precision with which a function (of one or more variables) matches a set of experimental data, extrapolating and interpreting values, is *RMSE* (root mean square of errors). The root-mean-square deviation (*RMSD*) or you can say root-mean-square error (*RMSE*) (or sometimes root-mean-squared error) is sometimes a used measure of the differences between data (sample and population values) predicted by a model or an estimator and the values actually observed. If a function  $y = f(x_1, x_2, \dots, x_n)$ , then  $y_i, i = \overline{1, n}$  the values obtained from  $n$  experimental samples and the value estimated by calculating the function  $f$  that analytically analyzes the process or phenomenon.

$$RMSD = \sqrt{\frac{\sum_{i=1}^n (\hat{y}_i - y_i)^2}{n}} \quad (4)$$

With root-mean-square error car being closer to zero, the function found is an analytical mathematical model better for a phenomenon, process, or mathematical relationship. In general, a  $RMSE < 0.05$  for a set of medical data is considered to be the result of a performance model. With root-mean-square error car being closer to zero, the function found is an analytical mathematical model better for a phenomenon, process, or mathematical relationship. In general, a  $RMSE < 0.05$  for a set of medical data is considered to be an excellent result of a performance model. In our case  $RMSE \approx 0.053$ , a good results better than the linear model and in the row with best results from state of the art presented in introduction. The successful classification has a rate of  $(33 \times 100) / 35 \approx 94.28\%$ .

### Conclusions

An evolutionary method, genetic programming was proposed to construct a mathematical function to estimate the state of the patient possible affected by Pubalgia . From 35 patients, only two cases were classified wrong, but the value of formulas was very close to the threshold between the classes. The further research will be conducted over a larger lot of patients and further refinement of the model expressed by mathematical function in order to have connections with physical phenomenon. This can be made by constraints over terminal and set of operators and possible depth of the trees. Also, more than three classes can be used in order to find a fine granulation of the e-health index value but this must be validated by medical assertion. The tool can be used as an automatic evaluator for monitoring the effectiveness of rehabilitation progress in treatment of Pubalgia and also as an evaluator of health after surgical intervention. The analysis of structural formulas can be used in the further research to evaluate the qualitative level of influence in health score of each variable. Depending on this value, some variables can be added to new analysis and other that have minor influence can be weighted with a lower value. It is also possible to eliminate some variables that have too lower influence in the evaluation of health process. In this way the clinical practice can be improved

### Author contributions.

All the authors had the same contribution.

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## Dorsalgia rehabilitation in static disorders of the spine by therapeutic swimming in young adults



WEB OF SCIENCE

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### Abstract

The purpose of this paper is to point out and propose the most effective means of therapeutic swimming in the use of work programs for patients with dorsalgia in spinal static disorders. The knowledge degree of therapeutic swimming is not sufficiently promoted and used, which is why we propose the following hypothesis: we start from the premise that therapeutic swimming can reduce the dorsalgia in the spine, improve lung capacity and physical condition in young adults. The objectives of this work are to identify subjects with spinal static dorsalgia and to establish the sample for the experiment; in the selection of therapeutic swimming means for the elaboration of the work program; in the registration and interpretation of the data in the form of tables and charts. The experiment took place at the Kinetic Therapy Practice of Mr. Constantinescu Mihai, as well as at the swimming pool in Cornisa, Botoșani county, with a sample consisting of 15 subjects aged between 18 and 22, all of whom suffered dorsalgia (in the spine). In this respect, we set out to implement a therapeutic swimming program for 6 months to achieve positive results.

**Keywords:** *dorsalgia, spinal static disorders, therapeutic swimming,*

### Introduction

Pain in the spine occurs in children, adolescents, adults, and it is a global concept that includes pain in the cervical, dorsal and lumbar spine (1).

Cervical pain is commonly found in adults, whereas the pain localized in the dorsal and lumbar levels is predominant in adolescents and young adults (2,3).

The incidence of dorsalgia is higher during the growing period, which is why the therapeutic intervention starts in school. Even if there are specific programs on maintaining health and preventing dorsalgia, they cannot change long-term behavior.

Dorsalgia involves sociodemographic, physiological, or psychosocial factors (4). Multifactorial concentration is essential especially in adolescence because most biomechanical and physiological parameters change during this growth period (5).

These changes are also found in the habits of adolescents who prefer to spend their free time in sedentary activities, with their friends, to the detriment of physical activity (6).

In this context, dorsalgia is influenced by sex and age (7).

The skeleton contains approximately 99% of the total calcium, whereas small amounts of it are found in the plasma and the extravascular fluid. Low calcium consumption can contribute to the appearance of rickets in children, to modifications in the physical development of the adolescent and later, of the young adult. This is why it is very important to know the normal calcium reference ranges, by age and sex groups (8).

Magnesium, together with calcium, plays an important role in muscle contraction, cardiac excitability, and insulin metabolism and it influences the vasomotor tone (9).

In this paper, we will address dorsalgia in spinal static disorders in patients between the ages of 18 and 22, the age at which the young adult is subject to a sedentary lifestyle, but also because of professions that overburden the body. Prolonged standing causes malalignments in the spine, whereas back pain occurs predominantly in the lumbar and cervical-thoracic areas. As regards the anatomically lumbar region, it is composed of 5 voluminous vertebrae, which are subjected to higher voltages than the other regions, and the cervical region is composed of

seven vertebrae and the thoracic region of 12 vertebrae, all of which are joined by intervertebral discs and related ligament structures. The muscles of the spine are also subject to continuous demands that can keep certain muscular stress called contracture, and if not treated properly it causes pain, functional impotence, and even some degenerative processes of morpho-functional structures.

It is known that due to the overuse and induced pressures on the spine, they react by modifying the body posture, by adopting vicious (antalgic) postures, which leads to the main physical deficiencies (kyphosis, lordosis, and scoliosis). Kyphosis has a sagittal spinal deviation with posteriorly oriented convexity; lordosis consists of a sagittal spine deviation with anteriorly oriented convexity, and scoliosis is a deficiency of the spine in the frontal plane with lateral convexity with a curvature or several ones.

In this regard, we will develop and implement a therapeutic swimming program in which to optimize the health condition, reduce spinal pain, and increase the effort capacity of patients who undergo the experiment.

The specialty literature shows that the morpho-functional, prophylactic, or therapeutic valences of swimming have been known since ancient times and have had continuity in various researches, by pointing out the benefits of swimming (10).

The influence of therapeutic swimming on muscular-skeletal structures causes joint mobility, toning, the stability of the spine with positive effects on the body posture (11); by adopting the horizontal position, positive influences of the osteoarticular system are exerted by favoring the reduction of pain mentioned by patients (12,13).

In the morpho-functional recovery, swimming induces demands to the body and causes positive modifications, which lead to the release of the spine from tension and favors the decrease of pain and the resumption of ADL (activity daily living). As for the cardiovascular system, the heart rate reaches the maximum values of 190-214 of b/min and returns to rest values in a few tens of minutes.

The German physiologists Dargatz and Koch (1995) considered that only one session of movement in the water can determine the increase in the physical yield of the maximum possibility of oxygen processing and vital capacity, During a session the alveolar-capillary diffusion increases (the gas

exchange at the alveolar level), but also the tissue breathing increases, thus increasing the percentage of myoglobin, while the respiratory volume per minute, the residual respiratory volume and the rest frequency decrease. To achieve the expected results, patients must be initiated into techniques specific to swimming (10).

**The purpose** of the work is to select the most effective means of therapeutic swimming, to reduce pain in the spine of the subjects included in the experiment.

### **Material and method**

The hypothesis of the work: it is assumed that therapeutic swimming can reduce the dorsalgia of spinal static disorders, improve lung capacity and physical condition in young adults.

### **Objectives of the work:**

- To identify subjects with spinal static dorsalgia and to determine the sample for the experiment;
- To select therapeutic swimming means for the elaboration of the work program;
- To record and interpret data as tables and charts.

The organization and conduct of the experiment: The selection of subjects for the experiment led to 15 subjects aged 18 to 22 that was done at the Private Practice of Kinetic Therapy Practice of Mr. Constantinescu Mihai, Suceava. For a period of about two weeks from 01.09.2020 to 16.09.2020, we observed and established the working sample, following the diagnosis given by the doctor (Mrs. Dr. Silisteanu Calina) to each patient. From 16.09.2020 to 31.09.2020 at the same location, the work program was carried out on land, using the therapeutic swimming technique. From 01.10.2020 to 28.02.2021, the program was carried out at the swimming pool in Cornisa, Botoșani county. The frequency of the water training was for an hour twice a week.

The study was conducted according to the ethics rules in force.

Selection criteria: persons aged 18-22, without acute or neuropsychic disorders, and who gave their consent to participate in the study.

Exclusion criteria: people aged <18 and > 22, with chronic respiratory, cardiac, digestive, or neurological diseases and who did not want to participate in the study.

Exercise program applied to the target group:



Getting used to the water: front swimming, rear swimming, walking through the water by moving the arms near the body, then bent from the elbow joint; diving; games.

**1<sup>st</sup> Stage:** To reduce pain, to install and to keep a correct attitudinal reflex that ensures the recovery of the pelvis, torso, and lower limbs during the static and dynamic activity.

- at the edge of the pool with hands against the edge, movements of the feet with the face on the water, and after 6 feet movements breathe in, on one side, 3x; floating on the water, feet movements, crawl and breaststroke on different distances, 2x7;12,5; 25m; feet movements backward, floating face on the water, arms held in the extension of the head 2x12,5; 25m; feet movements with hands held behind the head 7; 12,5 m; double swimming on the back 7; 12,5; 25m.

**2<sup>nd</sup> Stage:** The recovery of the spine, mobility, muscle toning, stability.

- forward rollovers or forward turns 3x; from swimming crawl with rolling forward at 12,5m; feet movements crawl, with arms near the body 2x7m; face on the water feet movements 2x 7; 12,5 m; from sliding, movements of arms 3x7m.

**3<sup>rd</sup> Stage:** The improvement of the parameters of cardiorespiratory function and effort capacity.

- swimming crawl on different distances 2x12,5; 25; 75, 100 m; swimming on the back on different distances 3x 12,5; 25; 75, 100; 150 m; breaststroke swimming on different distances 12,5; 25; 75, 100 m; freestyle swimming on different distances 2x 7 and 12.5 m

## Results and discussions

Dorsalgia was evaluated by using the VAS analog scale (0-10 mm). Other followed parameters were respiratory frequency and heart rate. (Table no 1)

In the test "VAS scale" test, it is easy to see: the average of the group at the initial test is 6.47, which shows that the patients' spinal dorsalgia cannot be ignored for a very long time, whereas the average of the group at the final test is 3.13, which indicates that the therapeutic swimming program was effective, the pain can be ignored if patients are involved in the daily work. (Figure no 1)

In the respiratory frequency test, the average of the group at the initial test is 17.87 cpm, at the final test, the average is 17,60 cpm at rest, if we talk about the respiratory frequency in an effort, the average of the group at the initial test is 21.13 cpm, and the average

of the group at the final test is 19.67 cpm, with a difference of 1.47 cpm. (Figure no 2)

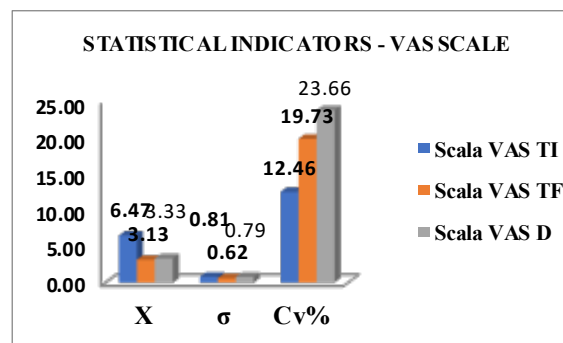


Figure no. 1 VAS Scale

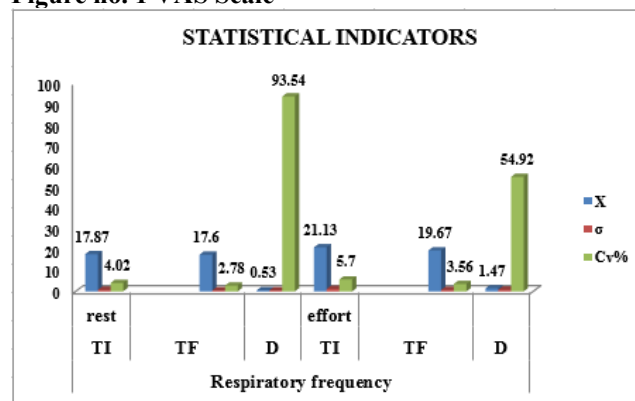


Figure no. 2 Respiratory frequency

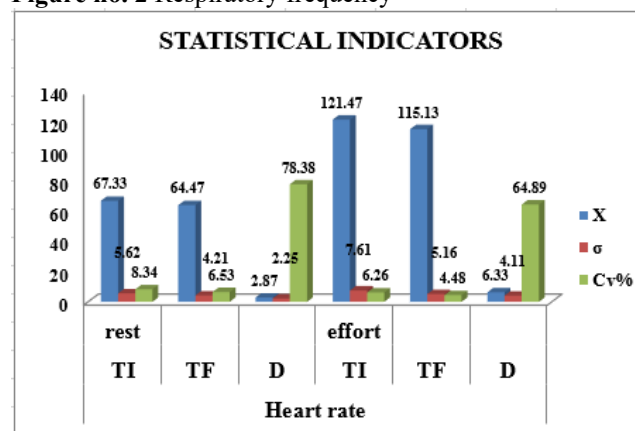


Figure no. 3. Heart rate

In the heart rate test, the average of the group at rest is 2.87 b/min, and the average of the group in the effort is 6.33 b/min with a difference of 6.33 b/min. (Figure no 3)

As for the test Chin sternum index in flexion, the average of the group between the initial test and the final one is 1.20 cm. In the same test, but in extension, the difference of the average is 1.07 cm. In the test Tragus-acromion left index, the difference between the initial test and the final one is 3.80 cm. In the same test but the one on the right, it is easy to see a difference of 2.67 cm. (Figure no 4,5)

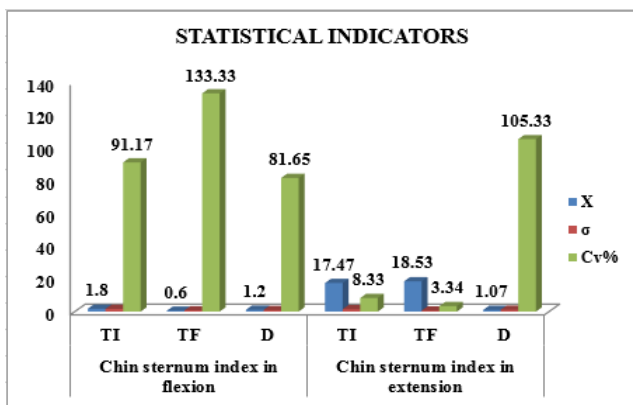


Figure no. 4 Chin sternum index

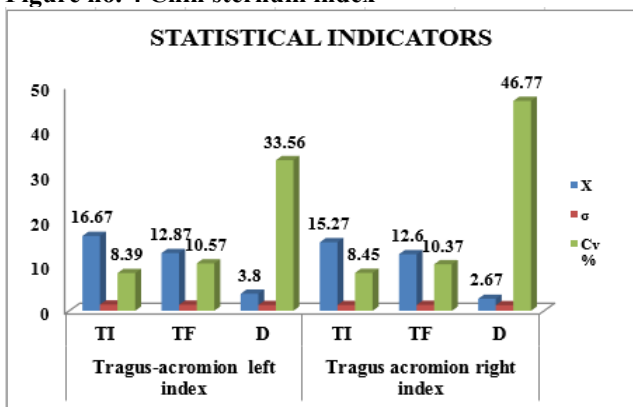


Figure no. 5 Tragus-acromion index

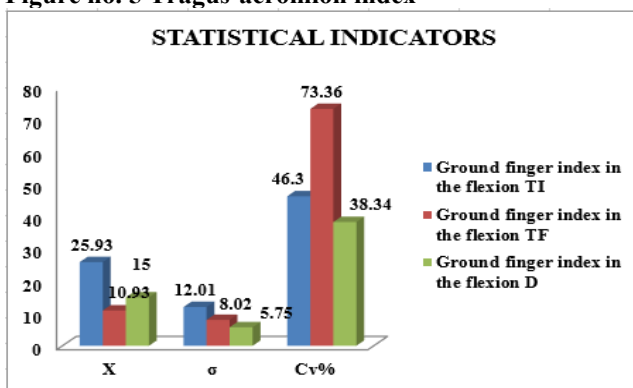


Figure no. 6 Ground finger index

In the Ground finger index test, there is a difference between the initial test and the final one, an average of 15,00 cm. (Figure no 6)

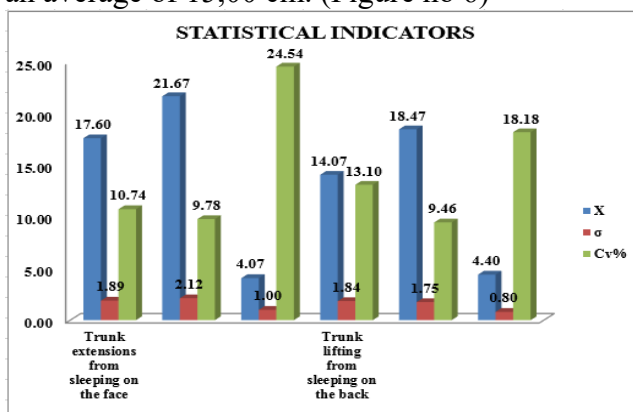


Figure no. 7 Trunk extensions/ lifting

In the Trunk extensions from sleeping on the face test, there is a difference of the average of 4.07 rept/20sec. In the Trunk lifting from sleeping on the back test, there is a difference of the average of 4.40 rept/20 sec.(Figure no 7)

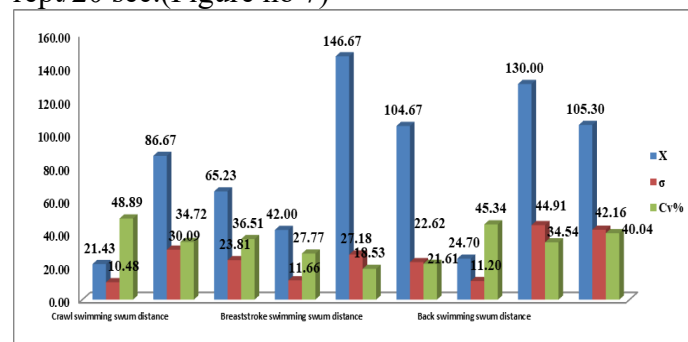


Figure no. 8 crawl, breaststroke, back swimming

In tests specific to swimming, there is a difference of the average between the initial test and the final one of 65.23 m in the crawl swimming. In the back swimming, the difference of the average is 105.30 m, whereas in the breaststroke type, the difference of the average is 104.67 m.(Table no 3 and Figure no 8)

## Conclusions

The hypothesis of this paper was confirmed by the fact that therapeutic swimming can optimize health, reduce back pain and improve patients' lung capacity.

Where the tests show a  $p < 0.05$ , the statistical link is significant (S, 95% confidence) and when the tests show a  $p < 0.01$ , the statistical link is significant (S, 99% confidence).

Of all the therapeutic swimming means applied to patients with spinal static dorsalgia, the means of dorsal decubitus were the most effective and most agreeable ones.

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**Table no.1. Functional indicators**

N=15	VAS SCALE			Respiratory frequency						Heart rate					
				cpm						No. b/min					
				rest			effort			rest			effort		
	TI	TF	D	I	F		I	F		I	F		I	F	
X	6.47	3.13	3.33	17.87	17.6	0.53	21.13	19.67	1.47	67.33	64.47	2.87	121.47	115.1	6.33
$\sigma$	0.81	0.62	0.79	0.72	0.49	0.5	1.2	0.7	0.81	5.62	4.21	2.25	7.61	5.16	4.11
Cv%	12.46	19.7	23.66	4.02	2.78	93.54	5.7	3.56	54.92	8.34	6.53	78.38	6.26	4.48	64.89
	t=2.52999 p<0.01			t=0.164318 p<0.05			t=2.84917 p<0.01			t=0.000297 p<0.05			t=4.88293 p>0.001		

**Table no. 2. Joint balance**

N=15	Index menton stern			Index menton- stern			Index tragus -acromion			Index tragus-acromion			Index finger- ground		
	in flexion			in extension			left			straight			in flexion		
	TI	TF	D	TI	TF	D	TI	TF	D	TI	TF	D	TI	TF	D
X	1.8	0.6	1.2	17.47	18.53	1.07	16.67	12.87	3.8	15.27	12.6	2.67	25.93	10.93	15
$\sigma$	1.64	0.8	0.98	1.45	0.62	1.12	1.4	1.36	1.28	1.29	1.31	1.25	12.01	8.02	5.75
Cv%	81.17	133.33	81.7	8.33	3.34	105.33	8.39	10.57	33.56	8.45	10.37	46.77	46.3	73.36	38.34
	t=0.00042 p<0.05			t=0.00318 p<0.05			t=2.39279 p<0.01			t=1.36946 p<0.05			t=1.26066 p<0.05		

**Table no. 3. Strength indicators and tests specific to swimming**

N=15	Trunk extensions from sleeping on the face			Trunk lifting from sleeping o the back (number of repetitions 20/sec)			Crawl swimming swum distance (m)			Breaststroke swimming swum distance (m)			Back swimming swum distance (m)		
	(number of repetitions 20/sec)			repetitions 20/sec)			(m)			(m)			(m)		
	TI	TF	D	TI	TF	D	TI	TF	D	TI	TF	D	TI	TF	D
X	17.6	21.67	4.07	14.07	18.47	4.4	21.43	86.67	65.23	42	146.67	104.67	24.8	130	105.3
$\sigma$	1.89	2.12	1	1.84	1.75	0.8	10.48	30.09	23.81	11.66	27.18	22.62	11.2	44.91	42.16
Cv%	10.74	9.78	24.54	13.1	9.46	18.18	48.89	34.72	36.51	27.77	18.53	21.61	45.34	34.54	40.04
	t=1.04049 p<0.05			t=2.50544 p<0.01			t=2.41132 p<0.01			t=1.41431 p<0.05			t=2.14612 p<0.01		



## Influence of the physical activity in the elderly people diagnosed with knee osteoarthritis during the pandemic period caused by COVID-19



WEB OF SCIENCE

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### Abstract

**Introduction.** Knee osteoarthritis is considered to be a chronic disease that affects the joints by causing pain, joint stiffness and decreased functional capacity. Regular physical activity can keep and increase functional capacity, it can reduce pain by improving movement behavior. The disruption of the sedentary behavior of the elderly patients with knee osteoarthritis can lead to improved physical function and general health. **The purpose** of this paper is to point out the role of physical activity in the elderly people diagnosed with knee osteoarthritis during the COVID-19 pandemic. **Material and method.** A total of 155 patients diagnosed (clinical and imaging) with knee osteoarthritis, who were treated on an outpatient basis, from May to September 2020, were studied. The parameters assessed in the study were pain, joint stiffness, the ability to carry out daily activities, anxiety and quality of life. **Results and discussion.** The studied group of patients was homogeneous in terms of the weight by age group and gender. Higher values were recorded in the study group in the evaluation of patients based on scales, the results being statistically significant, with value for  $p < 0.05$ , which means that the hypothesis was validated. **Conclusions.** Patients of the study group recorded improvement in functional capacity, joint stability and static and dynamic balance, which allowed a faster reintegration into the family and society.

**Keywords:** *physical activity, pain, elderly people, knee osteoarthritis,*

### Introduction

Knee osteoarthritis is considered to be a chronic disease that affects the joints by causing pain, joint stiffness and decreased functional capacity. The condition causes an important functional deficit, affecting posture, static and dynamic balance, walking (1).

Osteoarthritis is frequently accompanied by other diseases (respiratory, cardiovascular, diabetes, obesity, depression). Studies (2,3) show that 4 out of 5 people with osteoarthritis have at least another chronic condition, whereas the proportion of people with osteoarthritis by reference to comorbidity varies from 68 to 85%.

The factors that increase the risk of having osteoarthritis include age, sex, obesity, joint stress, but also some metabolic diseases, such as diabetes and hemochromatosis, a hereditary disease in which too much iron is absorbed and stored. In this context the quantitative determination of  $Fe^{3+}$  by the spectrophotometric method is the most commonly used due to the advantages (4).

In osteoarthritis, certain markers (C reactive protein, VSH) are correlated to the prognosis of the condition, so it is important that they are monitored (5).

The vast majority of the elderly patients diagnosed with knee osteoarthritis spend the day lying or sitting, do not do dynamic or locomotor activities (6). Over time, this behavior leads to other comorbidities, such as the cardiovascular ones (7,8).

Regular physical activity can keep and increase functional capacity, it can reduce pain by improving movement behavior. It can be evaluated, optimized and individualized according to sex, age, BMI, functional capacity, pain, comorbidities (9).

A study by Jugwa (2015) (10) pointed out the relationship between the sedentary behavior and the functional ability in the elderly people diagnosed with knee osteoarthritis, then concluded that the limitation of daily sedentarism (daily activities at home or outside it) and daily walking can improve functional capacity and reduce pain. It was found that the patients in the study were sedentary about 2/3 of the daily time whereas the speed of their walking movements was very slow.



The elderly people consider that knee osteoarthritis is a progressive, incurable disease that causes wear and tear over time (11). Thus, patients focus on pain and consider that physical exercises are no longer useful (12) and moreover, they affect the joints (13).

Therefore, the refusal to do any physical activity of low-moderate intensity (14) and in addition, the vast majority of the elderly correlate physical activity to pain (15).

However, many patients consider that pain correlates to the destruction of the joints caused by physical exercises (16).

Zhaoyang 's 2020 study (17) also shows that the lack of physical activity in the elderly people diagnosed with knee osteoarthritis causes chronic pain to persist in these patients. This study showed that the pain increased especially in the morning, which made patients to have sedentary behavior, so they did not do physical activity on the day with moderate pain. The study suggests that physical activities influence the sedentary behavior with medium and long-term benefits in order to manage pain, functional capacity and the quality of life.

The disruption of the sedentary behavior of the elderly patients with knee osteoarthritis can lead to improved physical function and general health (18). In this context, it is important to take into account the risk factors that may limit the physical activity: age, sex, BMI, pre-existing knee injuries (19). BMI was negatively correlated to walking and the number of steps taken daily. The recovery of these patients is based on behavioral interventions (20) that try to encourage movement, even if pain is present from the beginning, and the awareness of the fact that it will diminish over time. By establishing scientific education, it is possible to change the significance of pain from tissue damage marker to the need to protect the body from a danger that can be real or only perceived (16). This scientific education of pain can be considered as the basis of a biopsychosocial model of pain, disability and sensitivity, even if pain persists.

Changing the perception of pain by the patient actually means modulating pain, which is a protection feature of our system. It is necessary to distinguish between nociception and pain, regulating the mechanisms of the brain that enable the protection. Physical activity decreases "the hyperprotection of the body" imposed by the nervous system (21).

Physical exercise programs can generate positive effects on pain and functional capacity in comparison to taking simple analgesics or oral pills (22 ) but with reduced adverse reactions.

Physical activity is a multidimensional and complex phenomenon that requires a complex biopsychosocial approach (23), which enables understanding the characteristics of individuals regarding the acceptance and maintenance of physical activity (24). In this

context, health should be analyzed from a holistic perspective, by understanding biological, social and psychological factors (25) that can induce a state of illness.

In the biopsychosocial model of health and disease, the biological, social and psychological components are not considered independent, but they interact with each other (26). In fact, physical activity is a form of body movement integrated into the daily routine. Nowadays the recovery goals in the knee osteoarthritis are to reduce pain, inflammation, to increase the quality of life and to improve physical function (27).

International clinical guidelines recommend that the first line of treatment in knee osteoarthritis is the loss of weight, supplemented by physical exercise. It has a role in the muscle toning (28) to relieve pain, to increase the muscle strength and functional capacity, being useful in the postural control, proprioceptive and coordination (29).

Physical activity, according to WHO is considered a multidimensional behavior that includes the frequency of the activity, the intensity of execution, the execution time and the type of done exercise. The protective or destructive effect seems to depend on the intensity, type and frequency of physical exercise (27), which demonstrates the importance of all the components.

The physiotherapy program structured on education and neuromuscular exercise showed short-term statistical improvements in pain and functional capacity in comparison to the usual program. In the long term, there has been an increase in the daily activities and quality of life.

It was found that demographic, physical, psychosocial and environmental factors negatively influenced the physical activity of people with knee osteoarthritis (30).

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, (31) is at increased risk for the elderly people. The important prognostic factors are age, male sex, the presence of comorbidities (high blood pressure, diabetes, kidney diseases, respiratory diseases) (32). For the elderly who live alone and who also have comorbidities, supervision is necessary in order to ensure compliance with pharmacological treatment, nutrition, emotional state and last but not least, mental health (33). The COVID-19 pandemic, by introducing lockdown, quarantine, influenced the state of health, social relations and some activities (34). Quarantine and confinement are associated to stress, anxiety, depression, leading to reduced physical activity, to the modification of diet that has become low in vitamins and antioxidants (35).

For health, even during the pandemic period, it is essential to do regular physical exercise, 30-45 min/day, 3-5 times/week. In order to achieve the best results, the exercise program must take into account the type of exercise, the work intensity, the time of doing physical

activity. Thus, the type of physical exercise with resistance and aerobic regime can decrease the risk of infection and stimulate the immune system (36), on condition it is not for a very long period and it is not stressful (37,38).

It is recommended to do activities that can take place inside the domicile - relaxation, meditation, yoga, walking in the house, even fast walking, climbing stairs, jumping, squats, cycling- all carried out according to the functional capacity of each person and the presence of comorbidities.

If outdoor activities are allowed, it is necessary to keep the physical distance and according to the season, people can go walking, jogging, cycling, do gardening activities, family games, by complying with hygiene rules (39).

**The purpose** of this paper is to point out the role of physical activity in the elderly people diagnosed with knee osteoarthritis during the COVID-19 pandemic.

**Material and method.** A total of 155 patients diagnosed (clinical and imaging) with knee osteoarthritis, who were treated on an outpatient basis, from May to September 2020, were studied.

The objectives of this study were: to reduce pain, to keep and improve the functional capacity in the knee joints, to correct the alignment in the lower limbs, to re-educate static and dynamic balance and to re-educate gait.

The study complies with the rules of ethics and deontology according to the legislation in force.

The parameters assessed in the study were pain, joint stiffness, the ability to carry out daily activities, anxiety and quality of life.

For this, the visual analogue scale (VAS 0-100 mm) and the WOMAC subscale were applied for the pain assessment, the WOMAC subscale for joint stiffness and for the assessment of daily activities. For the assessment of general anxiety and disease-related anxiety, the S.T.A.I.-X2 and S.T.A.I. X-1 scales were used, whereas the QOL (Quality of Life) scale was used for the patients' quality of life.

The patients received treatment according to clinical guidelines, namely pharmacological treatment by nonsteroidal anti-inflammatory medication (applications on bones and local topic), antialgic, gastric, neurotrophic and decontracturant protectors.

The electrotherapy treatment included low-frequency currents (TENS-rectangular current, with antalgic role, with a frequency between 15-200 Hz, it acts by presynaptic inhibition and releases endorphins), medium frequency (interferential- with mainly analgesic action, vasomotor, hyperemic and secondary trophic, myorelaxant, in modulation 0-100 Hz in order to enable inhibitory and excitatory effects), ultrasound (a form of coupling-ultrasonophoresis with anti-inflammatory gel, for analgesic, hyperemic, myorelaxant, application in impulse mode in order to eliminate the thermal effect, the

frequency of 1 MHz, the intensity of 0.7W/cm<sup>2</sup>, for 5 minutes) (40).

Kinetic therapy consisted of sessions lasting 30 minutes/day, 3 times/week, for 4 weeks. The kinetic therapeutic program aimed at keeping and increasing joint mobility, trophicity (active exercises throughout the movement amplitude), keeping and increasing muscle strength, exercise training (free exercise, walking exercises, increase in general endurance), static and dynamic respiratory techniques, effort dosage exercises.

As for the occupational therapy, the objectives were to re-educate mobility, to enable locomotion and family and social reintegration. The following exercises were done: progressive transfer, dorsal-decubitus lateral-decubitus, lateral decubitus-sitting, sitting-orthostatism, then climbing /descending stairs, bending and rotating the trunk, doing domestic and recreational activities.

The evaluation of the patients was made in the beginning (M1) and at the end of the recovery treatment (M2), as well as at the control 6 weeks after its completion (M3).

The inclusion criteria were: the age over 60, clinical diagnosis and imaging of knee osteoarthritis, without decompensated and neurological conditions, who agreed to participate in the study. The exclusion criteria were: patients aged less than 60, with diseases of the respiratory and cardiovascular system in the decompensated stage, with neuro-psychiatric disorders, non-compliant patients, and who did not wish to participate in the study.

The patients were divided into two groups as follows:

- the study group who received pharmacological treatment, electrotherapy and physical therapy
- the witness group who received pharmacological treatment and electrotherapy.

The study group involved 76 patients: 40 (57.75%) were male and 36 (42.25%) female. The control group had 79 patients of which 38 (48.65%) male and 41 (51.35% female).

Table no. 1. Distribution of patients by groups

GROUP	Sex	60-69 years	70-79 years	> 80 years	Total
Study group	Male	16	13	11	40
	Female	15	13	8	36
Control group	Male	15	13	10	38
	Female	16	14	11	41
TOTAL		62	53	40	155

### Statistical analysis

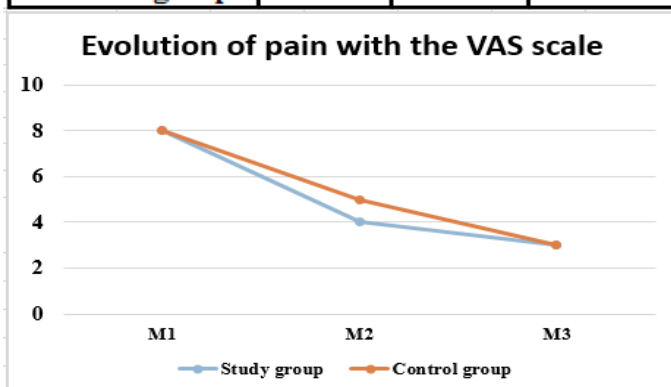
The data that was obtained from the initial, final and control assessments was processed statistically by using Microsoft Excel 10. Thus the median, the standard deviation and the t-student test were calculated in order to test the work hypothesis. It was chosen the level of statistical significance of 5%, so p should be less than 0.05 (p <0.05).

## Results

The pain assessed by the VAS scale decreased in the study group by 42.85% at the end of the treatment and 14.28% at the control, in comparison to the control group whose pain reduction was 37.5% at the end of the treatment and 25% at the control.

**Table no. 2.** Evolution of pain with the VAS scale

Scale VAS	M1	M2	M3
Study group	7±0.84	4±1.17	3±0.93
Control group	8±1.61	5±1.15	3±0.88

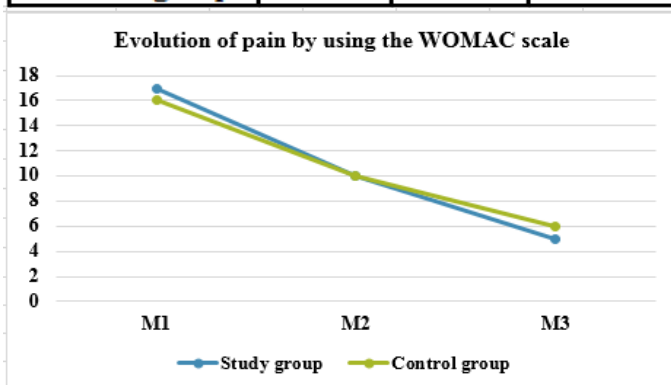


**Chart no. 1.** Evolution of pain with the VAS scale

The pain parameter assessed with the WOMAC subscale shows a decrease of 41.17% in the study group in comparison to 37.5% in the control group at the end of the treatment. During the control, the decrease is 29.41% in the study group versus 25% in the control group.

**Table no. 3.** Evolution of pain by using the WOMAC scale

Scale WOMAC	M1	M2	M3
Study group	17±1.17	10±0.11	5±0.25
Control group	16±1.51	10±0.71	6±0.49

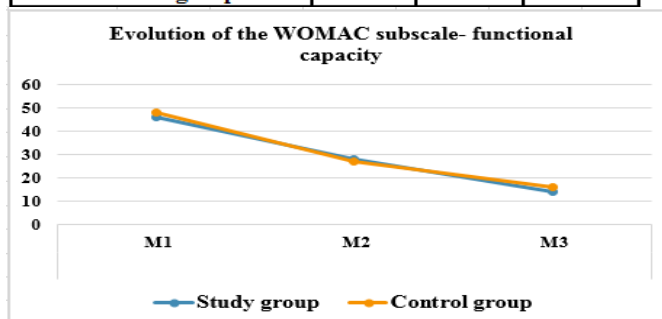


**Chart no. 2.** Evolution of pain by using the WOMAC scale

As for the functional capacity for daily activities, there was an increase in the abilities of 39.15% in the study group while completing the treatment and 30.43% in control, whereas in the control group this increase was 43.75% at the completion of the treatment and 22.91% at the control.

**Table no. 4.** Evolution of the WOMAC subscale- functional capacity

The WOMAC subscale	MOMENT		
functional capacity	M1	M2	M3
Study group	46±4.01	28±0.38	14±0.53
Control group	48±5.40	27±3.37	16±1.52



**Chart no. 3.** Evolution of the WOMAC subscale- functional capacity

The WOMAC score, representative of the arthrosis phenomenon, allowed an overall assessment of patients with knee osteoarthritis and an increase of 38.57% at the end of the treatment and 30% at the control group, and in the control group of 43.05% at the end of the treatment and 22.22% at the control.

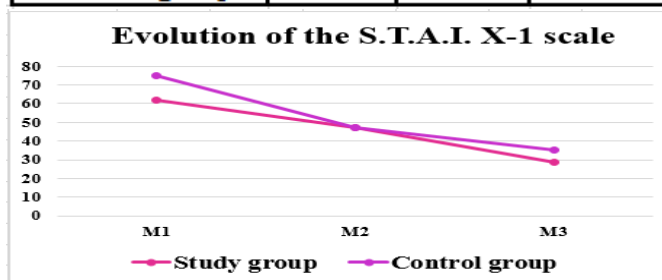
**Table no. 5.** Evolution of the WOMAC scale

Scale WOMAC	M1	M2	M3
Study group	70±4.30	43±2.28	22±0.41
Control group	72±6.14	41±3.56	25±1.54

Anxiety as a condition caused by registered knee osteoarthritis, with the S.T.A.I.-1 scale, the decrease in anxiety by 24.19% at the end of the treatment and 29.83% at the control. In the control group the reduction of anxiety as a state was 37.3% at the end of the treatment and 16% at the control.

**Table no. 6.** Evolution of the S.T.A.I. X-1 scale

Scale S.T.A.I.-X1	M1	M2	M3
Study group	62±2.83	47±4.56	28.5±1.81
Control group	75±1.13	47±5.35	35±2.26



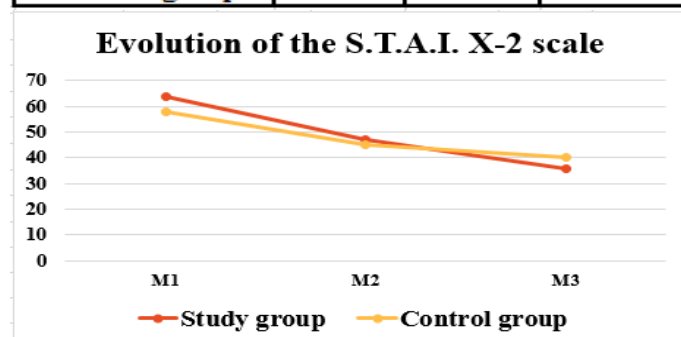
**Chart no. 4.** Evolution of the S.T.A.I. X-1 scale

As for anxiety as a general condition (caused by comorbidities, quarantine/confinement during the pandemic period, emotional states of patients), it registered a reduction in the study group of 26.56% at the end of the treatment and 17.18% at the control, in comparison to the control group where the reduction

was 22.41% at the end of the treatment and 8.62% at the control.

**Table no. 7.** Evolution of the S.T.A.I. X-2 scale

Scala S.T.A.I.-X2	M1	M2	M3
Study group	64±3.62	47±2.91	36±1.07
Control group	58±6.95	45±3.58	40±1.28

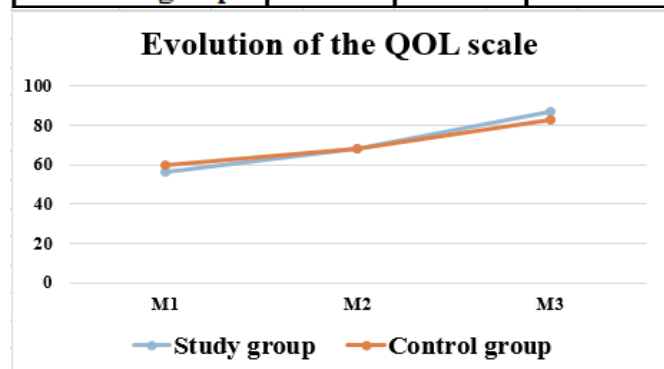


**Chart no. 5.** Evolution of the S.T.A.I. X-2 scale

Patients' quality of life improved. Thus, at the end of the treatment there was an increase in their quality of life of 13.79% in the study group in comparison to 9.64% in the control group, and at the control the increase was 21.83% in the study group and 18.07% in the control group. At the control in comparison to the beginning of the treatment, the quality of life improved by 35.63% in the study group and by 27.71% in the control group.

**Table no. 8.** Evolution of the QOL scale

Scale QOL	M1	M2	M3
Study group	56±7.57	68±8.51	87±9.48
Control group	60±4.24	68±3.52	83±1.99



**Chart no. 6.** Evolution of the QOL scale

## Discussion

The studied group of patients was homogeneous in terms of the weight by age group and gender. Higher values were recorded in the study group in the evaluation of patients based on scales, the results being statistically significant, with value for  $p < 0.05$ , which means that the hypothesis was validated.

**Table no. 9.** T-student test values in the study group

Scale/Moment	M1-M2	M2-M3
SCALE VAS	0.0483	0.0207
Subscale WOMAC-pain	0.0341	0.0498
Subscale WOMAC-stiffness	0.0159	0.0363
Subscale WOMAC-fct. capacity	0.0315	0.0489
Scale WOMAC	0.0295	0.0097
Scale S.T.A.I. X-1	0.0128	0.0097
Scale S.T.A.I. X-2	0.0061	0.0094
Scale QOL	0.0039	0.0051

In the group who also received kinetic therapy, the results are better, as it is shown by the published articles and which show that the physical exercise done regularly by the patient is a means of reducing pain, a way of increasing mobility, improving the quality of life and decreasing the anxiety state.

Thus Stranton's study (41) of 2020 shows that the treatment of individualized kinetic therapy and the education of the patient to manage pain led to the reduction of the pain and the improvement of the functional capacity.

Physical activity (14) prevents impairment of the physical capacity of the elderly patients diagnosed with knee osteoarthritis and keep their functional independence.

In the control group, after the application of the t-student test, the results are statistically significant for the VAS, WOMAC, QOL scales for all the assessment moments, except for the Womac scale for stiffness, the final moment-control, at which  $p > 0.05$ , as shown in Table No. 10.

**Table no.10.** Evolution of the t-student test for the evaluation parameters in the control group

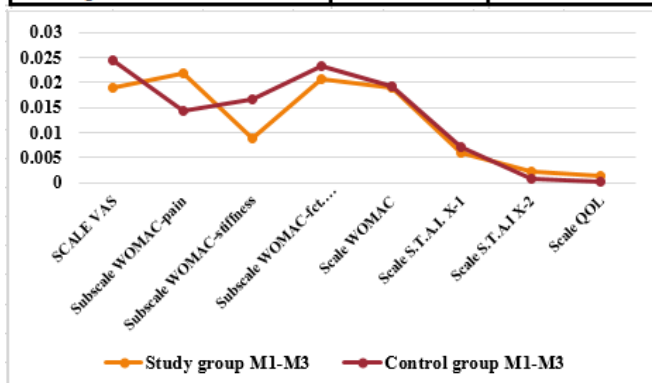
Scale/Moment	M1-M2	M2-M3
SCALE VAS	0.0389	0.0491
Subscale WOMAC-pain	0.0295	0.0331
Subscale WOMAC-stiffness	0.0231	0.0509
Subscale WOMAC-fct. capacity	0.0441	0.0381
Scale WOMAC	0.0399	0.0318
Scale S.T.A.I. X-1	0.0102	0.0023
Scale S.T.A.I. X-2	0.0022	0.0052
Scale QOL	0.0061	0.0094

The results obtained at the t-student test between the initiation time of the treatment (M1) and the control time (M3) show significant statistical results in the study group in comparison to the control group.



**Table no.11.** Evolution of the t-student test in both lots

GROUP/MOMENT	Study group	Control group
Scale/TEST t-student	M1-M3	M1-M3
SCALE VAS	0.0189	0.0243
Subscale WOMAC-pain	0.0219	0.0144
Subscale WOMAC-stiffness	0.0089	0.0167
Subscale WOMAC-fct. capacity	0.0207	0.0233
Scale WOMAC	0.0188	0.0191
Scale S.T.A.I X-1	0.0059	0.0071
Scale S.T.A.I X-2	0.0023	0.0007
Scale QOL	0.0012	0.0003



**Graph no. 7.** T-student test in the 2 groups

Patients have been recommended to continue at home the exercise program made in the physiotherapy rooms and as much as possible to carry out other activities such as recreation, gardening. It was also indicated to walk, to cycle to , depending on the functional capacity of each patient.

### Conclusions

The application of the treatment was individualized and it took into account the stage of the disease, algic symptomatology, the patients' mobility capacity, the emotional state caused by the COVID pandemic -19.

By applying the combined treatment with electrotherapy and physiotherapy, in the study group it was found in addition to reducing pain and increasing mobility, joint function in comparison to the application of electrotherapy only in the control group.

And the anxiety state was significantly reduced in the group to whom physiotherapy was applied, whereas the improvement of the quality of life was also significant in this group.

Patients of the study group recorded improvement in of functional capacity, joint stability and static and dynamic balance, which allowed a faster reintegration into the family and society.

### Author contributions.

All the authors had the same contribution

### Accordance to ethics standards

The study complies with the rules of ethics and deontology according to the legislation in force.

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## Rehabilitation challenges in COVID-19 induced acute polyradiculoneuropathies

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### Abstract

**Introduction.** SARS-COV 2 infection causes damage of the peripheral nervous system: loss of smell loss of taste and demyelination or axonal injury in the spinal roots and motor and sensory nerves with acute polyradiculoneuritis. As many people are affected by COVID-19, the number of patients with secondary peripheral nervous system damage is increasing. **Material and method.** There are a significant number of Guillain Barre syndrome (GBS) cases reported in COVID-19 positive patients, leading to the recognition of GBS as one of the peripheral nervous system complications of SARS-COV 2 infection. We are trying to summarise the particularities of specific rehabilitation in post-COVID patients. **Results and discussions.** The rehabilitation of a COVID patients has particularities, first – because of infectious risk carried by the patient during the procedures, second by the patient’s pulmonary and physical impairments induced by the Coronavirus. **Conclusions.** There is scarce evidence for rehabilitation interventions, and many recommendations are based on methods developed in other viral infections or chronic pulmonary and neurologic conditions. There is a urgent need for studies regarding the efficacy of interventions in COVID rehabilitation, as the number of patients is constantly increasing.

**Keywords:** *therapeutic plasma exchange, plasmapheresis, neuroimmune disorders, rehabilitation,*

### Introduction

The most common clinical presentation in COVID patients is with respiratory symptoms, but neurological impairments are increasingly reported. Neurological manifestations have been described in a significant number of COVID patients, involving both central nervous system (CNS) and peripheral nervous system (PNS), and ranging from mild to severe symptoms (1). General neurologic symptoms as headache and dizziness were also reported (2).

Neurological symptoms associated with SARS-COV 2 infection have been described with different incidence by many studies. Mao L. identified neurological manifestations only in 36,4% of patients, with dizziness, headache and alterations in smell and taste been described as most common (3). Another study reported that up to 73% of hospitalized COVID patients have neurological manifestations (4).

### Peripheral nervous system involvement in COVID-19

Peripheral nervous system involvement in COVID-19 includes olfactory dysfunction (anosmia/hyposmia), gustatory dysfunction (ageusia), Guillain-Barré syndrome and variants (Miller Fisher syndrome), cranial nerves polyneuritis, facial palsies, and critical illness polyneuropathy (4). Incidence of PNS symptoms ranges between 8,9% and 13% in two observational studies (5, 6). Anosmia/hyposmia and gustatory dysfunction were the most common, and are encountered in variable incidences, ranging from 48 to 98% for olfactory dysfunction and to 71 to 88% for ageusia (7,8, 9, 10). Acute neuropathies are considered to be associated with SARS-COV 2 infection if their onset is within 6 weeks after the confirmation of COVID infection, when no other commonly associated causes were detected (1). The pathogenetic mechanisms of PNS damage are variable. Hyposmia and dysgeusia are most probably caused by direct viral damage of olfactory and gustatory



receptor cells, which express angiotensin-converting enzyme 2 (ACE-2) receptors (11). Another postulated mechanism for dysgeusia is the direct damage of the chorda tympani nerve, a sensory branch of facial nerve (CN VII) responsible for taste, during the nasopharyngeal and middle ear colonization by SARS-COV 2 (12). PNS complications of COVID-19 are the consequence of the neurotrophic properties of the virus, and of the immune-mediated injuries of cranial nerves and spinal roots (6,11). Also, critical illness-associated peripheral nerves damage contributes in the severe and critical cases to the PNS injury by specific mechanisms, such as the systemic inflammatory response syndrome (SIRS), cytokine release and microcirculatory damage (2). Moreover, PNS complications were more frequent and severe in COVID patients requiring intensive-care treatment (6).

#### **Acute polyradiculoneuropathies in COVID patients.**

Acute polyradiculoneuritis (PRN) or Guillain Barre syndrome (GBS) is a severe dysimmune disease, which requires early diagnosis and intensive management. Many reports of GBS associated with COVID-19 have been published, and GBS is emerging as an important associated disease in COVID patients, representing 7-8% of reported neurological manifestations (4). The overlap between respiratory dysfunction caused by neurologic impairment of respiratory muscles and respiratory failure induced by SARS-COV 2 makes the diagnosis of GBS critically important (13). The incidence of GBS in northern Italy showed an 2,6 fold increase during the COVID-19 pandemic peak, supporting the role of SARS-COV 2 in inducing acute polyradiculoneuritis (14). Another study conducted in the UK showed that the incidence of GBS cases remained unchanged during the pandemic year (15).

The onset of GBS symptoms was variable: in the first days after viral detection, concurrent with COVID-19 symptoms (so called "para-infectious" pattern), but also after the acute phase of viral infection ("the post-infectious" pattern – described in acute polyradiculoneuritis not associated with SARS-COV 2) (2). Other studies reported longer interval since viral detection and neurologic symptoms, ranging from 2 to 24 ±11 days, both para- and post-infectious GBS being reported (14, 16). The occurrence of concurrent neurologic symptoms in the acute phase of SARS-COV 2 infection is the consequence of an acute dysimmune attack against PNS during the "cytokine storm" (11). For the "post-infectious" pattern of SARS-COV 2 triggered GBS, a molecular mimicry mechanism between the viral protein-associated gangliosides and peripheral nerve gangliosides have been described (13).

The clinical presentation of PRN in COVID 19 patient is heterogenous; the typically ascending motor and sensory deficits with loss of deep tendon reflexes is the most common (more than 75% of patients had an ascending course); facial weakness and respiratory failure were also described (14, 16, 17). In an observational study of adult COVID-19 patients, the most common neurological symptom was motor weakness (in 34,4% of patients), with higher incidence (51%) in Intensive Care Unit (ICU) patients; tetraparesis was noted only in 15% of patients (6). In a systematic review, most common features of COVID-associated GBS were sensory symptoms in 72% of patients, para- or tetra-paresis in 65%, cranial nerves involvement in 16%, areflexia in 10% and gait ataxia in 37,5%. Only 16,7% of patients developed autonomic symptoms. Mean age of the patients was 55 years, with male predominance (17). Compared to COVID negative GBS patients, COVID – positive GBS patients had a more severe motor deficit, a more frequent involvement of all four limbs, and they were more predisposed to be admitted in the ICU (14).

Among the 3 main subtypes identified based on electrophysiological features, the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most frequent, affecting 66 to 77% of patients, the axonal variants (acute motor axonal neuropathy - AMAN, acute motor sensory axonal neuropathy - AMSAN and Miller-Fisher syndrome - MFS) accounting for the rest (between 6,7 to 34%) (13, 14, 17). The cerebrospinal fluid (CSF) studies showed typical albumino-cytological dissociation in 71% of patients (17). Despite elevated protein levels, most studies reported negative PCR test for SARS-COV 2 in the CSF, supporting the immune-mediated pathogenetic mechanisms (16).

An UK study showed that the neurological recovery prognosis in COVID-associated GBS is similar to non-COVID GBS (15). In COVID positive patients, favourable prognosis occurred in 72% of patients with GBS, 10 % had no clinical improvement, 11,8% required ICU admission and 5,8% died (17). One fifth of patients required mechanical ventilation. It has been hypothesized that ventilatory support in COVID-related GBS was also required due to viral-induced pulmonary damage, not only to neuromuscular weakness (15, 18). Patients with poor outcome were older and had a severe form of COVID-19 (17). The modified Erasmus GBS Outcome Score (mEGOS) is an useful tool designed to assess GBS prognosis, predicting long term outcome of patients based on their clinical presentation at day 7 after admission (19). The mEGOS scores did not show any statistically significant difference between COVID-induced and "classical" GBS (13). Also, mortality was 11% in GBS related to SARS-COV 2 infection, identical to classical GBS.



## **Rehabilitation interventions in acute polyneuropathies**

Regardless of the cause, GBS is an important cause of long-term disability, requiring a wide range of rehabilitation interventions (20). After the acute phase, it was reported that approximately 40% of patients require intensive inpatient rehabilitation, and in the chronic phase 16% of patients are still reporting limitations in work and social activities (20). At 6 months after GBS onset, 20% of patients required help or assistive devices for walking. The most frequent deficits in acute PRN survivors are motor and sensory deficits, fatigue and pain (21).

Rehabilitation methods proposed for GBS patients before COVID pandemic include multidisciplinary rehabilitation and specific interventions. Multidisciplinary rehabilitation delivered patient-centred, functional-oriented and coordinated interventions by two or more disciplines: physiotherapy, occupational therapy, nursing, psychological counselling or social support, provided in inpatient settings, or ambulatory (20). Physiotherapy techniques are addressed especially to mobility impairments: maintenance of postures, joint range of motion exercises, endurance training, muscular strengthening and reinforcement, cycling, progressive ambulation programs. Also, physiotherapy programs should be non-fatiguing, and should avoid muscle groups overworking (20). The use of assistive devices, orthoses and ambulatory aids should optimise the gait and the motor function. Occupational therapy focuses on reacquisition of skills required for patient autonomy, use of adaptative equipment or environment changes.

## **Rehabilitation interventions in COVID patients with PNS impairments**

Patients with severe COVID infection usually recover with sequelae in multiple systems: respiratory, cognitive or neurological, associated with deconditioning; all dysfunctions should be addressed by specific interventions (22). In patients recovering after COVID-19, rehabilitation of neurologic sequelae is not possible without concomitant rehabilitation of respiratory function and of deconditioning. Another important challenge is that COVID patients recovering from severe forms could be potentially unstable and had a low exercise tolerance. For that reason, monitoring of heart rate (HR), respiratory rate (RR) and oxygen saturation (SaO<sub>2</sub>) is mandatory during physical therapy. Patients which had moderate forms of SARS-COV 2 infection frequently showed fatigue and exercise intolerance, with decrease in oxygen saturation. Post-COVID sequelae should be considered in all patients, it was predicted that approximately half of discharged patients will need further rehabilitation support or social care (23).

There is a conflicting evidence regarding early rehabilitation for severe forms of SARS-COV2

infections. There are recommendations for starting early progressive rehabilitation programmes, within the first 30 days after diagnosis, for a maximal impact on recovery (23). Moreover, an international task force in the field of pulmonary rehabilitation recommended initiation of inpatient rehabilitation during the acute COVID infection, addressing immobility, muscle weakness or neurological impairment (24). In contrast, there are recommendations against early rehabilitation in severe COVID patients, because of the associated risk of rapid desaturation during exercises (25). The timing of respiratory rehabilitation should be individualized, depending on patient's status and comorbidities (26).

Before discharge, it is recommended to assess patient's oxygen needs during rest and during exercise. Also, patient's ability to perform physical exercises and his functional capacity should be assessed by simple tests, such as 6-minute walk test and 1 minute sit-to-stand test (27). After discharge, there is a strong recommendation for performing regular daily activities and for continuing low or moderate-intensity physical exercise during the first 6 to 8 weeks. After this interval, patient's limitations, needs and dysfunctions should be reassessed, and new rehabilitation goals should be established. Pulmonary sequelae were found at 6-8 weeks after discharge (mild to moderate restrictive dysfunction), but also after 1 year follow up (23). If persistent lung function impairment is identified, the patient will continue the comprehensive pulmonary rehabilitation programme, which includes exercise training, (respiratory muscle training, coughing exercises, diaphragmatic training, stretching exercises), patient education, psychosocial support, and behavioural modification strategies (23). If lower limb weakness or mobility problems are diagnosed, a muscle strengthening programme is recommended (24).

Rehabilitation of patients with COVID and associated GBS with pulmonary dysfunction is challenging. Usually, one third of GBS patients had respiratory dysfunction, caused by respiratory muscles weakness with incomplete recovery. Even before COVID pandemic, post-GBS respiratory dysfunction required specific interventions, such as breathing exercises, chest percussion or resistive respiratory training (20). In COVID-19 survivors, respiratory problems secondary to lung fibrosis are difficult to manage, requiring long rehabilitative interventions with specific physical therapy methods, such as endurance training or strengthening exercises (22, 28). For endurance training, the patient could use ground walking or an ergometric bicycle, with continuous HR, blood pressure (BP) and SaO<sub>2</sub> monitoring, until 60% of maximal HR or 80% of gait speed are attended after 6 minutes walking (28). Also, upper and lower limb exercises are recommended, depending of individual effort tolerance.

Breathing training exercises are, and many techniques were proposed: pursed-lip breathing, diaphragmatic control techniques, thoracic expansion techniques, training of thoracic respiratory muscles. The results obtained after respiratory rehabilitation should be monitored with specific scales: St-George Respiratory Questionnaire (29) and the 6 minutes walking test (30). Rehabilitation of post-COVID deconditioning is mandatory, and it will also improve respiratory functions, as well as GBS-induced muscles weakness. Interventions should include aerobic training, breathlessness management, energy conservation, with or without oxygen supplementation (31). Also, in chronic phase, stable patients with pulmonary dysfunction and neurologic impairments could benefit of specific balnear methods of rehabilitation and relaxation (32). In the pandemic context, virtual (remote) rehabilitation of COVID outpatients have been proposed. Tele-rehabilitation with a physiotherapist following the patient performing recommended exercises during a session, could be considered an useful tool in patient care, which maintain the connection between the patient and the medical team (33).

## Conclusion

As SARS-COV 2 continues to spread, more patients with associated neurologic symptoms, including acute PRN, will be diagnosed. Clinicians should be aware of the possibility of COVID-associated neurologic manifestations, detailed clinical and paraclinical investigations should be performed, and appropriate treatment and rehabilitation interventions should be recommended, concomitantly with specific COVID treatment. Recognition of these different entities is important for improving care for COVID patients. Rehabilitation is an essential tool in the management of complex, multisystem post-COVID dysfunctions. Until today, there are no researches relevant to rehabilitation in post-COVID patients. There is scarce evidence for rehabilitation interventions, and many recommendations are based on methods developed in other viral infections or chronic pulmonary and neurologic conditions. There is a urgent need for studies regarding the efficacy of interventions in COVID rehabilitation, as the number of patients is constantly increasing.

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## Challenges regarding rehabilitation treatment in a case of postpartum spastic paraparesis, secondary to a T9 vertebral fracture on the pathologically bone operated - case report



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### Abstract

**Introduction.** Pregnancy is a well-known risk factor for asymptomatic hemangiomas discovered incidentally, becoming aggressive or symptomatic, most often in the third trimester of pregnancy, related to hemodynamic and endocrine changes that occur during pregnancy. Many patients experience incomplete spontaneous remission after birth. **Material and method.** We report the case of a 24-year-old woman, who presented for incomplete paraplegia, pain in the spine, instability of walking of the left lower limb, bilateral plantar paresthesia, possible walking with metal support. **Results and discussions.** The MRI performed identifies T9 vertebral fracture-compression on pathological bone, T10-T12 vertebral hemangiomas. **Conclusions.** In order to obtain favorable results, the patient benefited from the support and treatment of a multidisciplinary team: neurosurgeons, imagers, physical and rehabilitation medicine doctors and physiotherapists, and represented a real challenge regarding the complexity of the factors involved.

**Keywords:** *hemangioma, rehabilitation, multidisciplinary team,*

### Introduction

The first description of vertebral body hemangioma was made by R. Virchow in 1867 (1). Probably the first description of the associated neurological manifestations, were presented by Gerhardt in Germany in 1895. However, only in 1926 Perman, then Bailey and Bucy - in 1929 described in detail the radiological characteristics, accepted even today, of vertebral hemangioma. Pregnancy is a well-known risk factor for asymptomatic hemangiomas discovered incidentally, becoming aggressive or symptomatic, most often in the third trimester of pregnancy, related to hemodynamic and endocrine changes that occur during pregnancy (2,3). Many patients experience incomplete spontaneous remission after birth (4). Hemangioma is the most common benign vertebral tumor, developing in the vascular endothelium, with slow growth (5,6). It is more common in postpubertal women, maximum morbidity (onset) is found in the 3<sup>rd</sup> decade of life (7,8,9). It is found extremely rarely in children, but with age it increases in size (10). It has been found that 10% of complicated vertebral fractures of hemangioma occur in pregnant women, the maximum activation taking place in the third trimester of pregnancy (11).

In 76% of cases, hemangioma affects the thoracic segment, preferably the T6 vertebral body, followed by the lumbar segment with preferential location in the L3

vertebral body, the cervical and sacral segments are affected very rarely (less than 1%) (12). It usually affects a vertebral body, but in 10-15% of cases it can be multiple - hemangiomatosis (13). The clinical picture is variable, from asymptomatic to pain and spinal cord compression (15,16).

Radiological images have a pathognomonic aspect: vertebral striations, which give the vertebral body an alveolar appearance, respecting the integrity of the cortical bone and the intervertebral disc (17,18). The treatment consists of classic or minimally invasive surgery with percutaneous vertebroplasty, alcoholization, embolization or radiotherapy treatment (19, 20).

### Material and method

We present a case of a woman 24-year-old, presented to the Techirghiol Balneal and Rehabilitation Sanatorium for motor deficit with incomplete paraplegia, pain in the spine, instability of the left lower limb, bilateral plantar paresthesias, possible with metal frame support. From the personal physiological and pathological antecedents, we remember an ovarian cyst operated, a birth by cesarean section-twin pregnancy (two months ago), vertebral compression fracture on pathological bone T9 operated, for which T9 cement vertebroplasty was performed and bilateral metal synthesis with transpedicular screws at T8,



T10 and interconnecting rods, laminectomy T9. During surgery, the left T9 root is resected as needed. From the patient's medical history, we remember multiple pregnancies with 3 embryos initially, later an embryo stopped evolving in week 5-6 of pregnancy. At week 10, the patient was diagnosed with low pregnancy, at risk of miscarriage, and was recommended bed rest. Week 20 coincides with the onset of back pain, with the palpation of a painful formation on the back. Following a specialist consultation, bed physiotherapy is recommended. The patient's symptoms are persistent, with paresthesias in the lower limb, intensified back pain in orthostatism and gait, improved in dorsal decubitus.

It is recommended by the specialist doctor after the clinical examination, to perform a spine MRI, but the patient refusing. The patient gave birth on time, by cesarean section, without medical problems. Postpartum, the symptoms were rapidly progressive, with the appearance of sensitivity disorders, with impaired tactile superficial sensitivity, painful and thermal with hypoesthesia in the bilateral lower limbs, but also with impairment of deep myo-arthro-kinetic and vibratory sensitivity, with poor perception of imprinted movements in the segments of the pelvic limbs. In addition to the appearance of sensitivity disorders, pain intensifies in the lumbar spine with irradiation in the pelvic limbs. Computer tomograph is performed in a private clinic and no imaging changes are identified, it is recommended to rest in bed, the pain being attributed to the weight gained during pregnancy. Subsequently, due to the altered general condition, the persistence of neuroradicular syndrome and sensitivity disorders, the patient addresses the Emergency Department of the County Hospital "Sf. Apostol" Constanța, and following clinical and magnetic resonance imaging (MRI) examinations the following diagnoses are made:

- T9 vertebral fracture-compression on pathological bone (vertebral hemangioma)
- T10-T12 vertebral Hemangioma
- Incomplete Frankel C paraplegia with T8 level
- Lower limb pressure
- Micturition disorder
- Anemia

Emergency hospitalization is recommended for surgery. Due to the complexity of the surgery, the transfer is decided in the Neurosurgery Department II of the Emergency Clinical Hospital "Bagdasar-Arsenie" Bucharest.

Clinical examination at presentation:

- Attitude: keep lying down -Walking and orthostatic: impossible
- Mobility: Frankel C with T8 level
- Cutaneous reflexes: indifferent bilateral plantar
- ROT: present, diminished lower limbs

- Sensitivity: sensitivity deficit with neurological level T8
- Sphincters: normal, without disorders
- Cranial nerves: I-XII normal clinical relations
- Psychic / Speech: oriented temporally-spatially and to one's own person

The MRI performed in the sagittal plane (Fig.1) shows: compression of the T9 vertebral body with cuneiform appearance, recoil of a bone segment at the posterior wall, intracanal posteroinferior with compressive effect on the dural sac, focal lesion of 6/7 mm with osteolytic character at the external 1/3 level and upper vertebral body T10. MRI examination, axial section (Fig.2): bone structure is inhomogeneous in the T9 vertebra (body, pedicles, transverse and spinous processes, upper and lower joint processes) by the presence of predominantly osteolytic lesions, associating the visualization of bone trabeculae, the appearance being suggestive for vertebral hemangioma. The surgery is decided, performed vertebroplasty with cement T9 and bilateral metal synthesis with transpedicular screws at T8 and T10 level and interconnecting rods, T9 laminectomy. The left T9 root is dried out of necessity, the dura mater remains intact.

### Discussions

Favorable postoperative evolution, without complications. She was discharged on time, and was referred to the medical rehabilitation service. Ten days after surgery the patient was transferred from the Neurosurgery Department, to the Medical Rehabilitation Service from Techirghiol Sanatorium, for incomplete paraplegia with T8 level, where she underwent a complex physical kinetic recovery treatment, in order to posture and re-educate the gait.

The patient was evaluated clinically, functionally (using the Frankel, Barthel scales, IADL / ADL index) and biologically, in dynamics to monitor the effectiveness of the neuromotor recovery program.

Clinical examination performed at admission shows:

- Temporally-spatially oriented patient, auto and allo psychic, cooperative, MMSE 30/30 test, without signs of meningeal irritation;
- Presents supple postoperative wound, healing, without signs of inflammation, at T8-T12 level (Fig.3) ;
- Increased abdomen of postpartum volume, flaccid (Fig.3) ;
- Static vertebral syndrome: the alignment and posture of the cervical spine lumbar back are analyzed both in the frontal plane and in the sagittal plane and the accentuation of the dorsal kyphosis is observed (Fig.3) with lumbar rectitude in the sagittal plane;
- Dynamic vertebral syndrome: limited mobility in all axes of movement;

- Musculoligamentar syndrome : bilateral lumbar paravertebral muscle contracture;
- Neuroradicular syndrome: back pain in prolonged sitting position and orthostatism, lumbar pain with irradiation in the pelvic limbs;
- Sketched proximal motor control, sketched intermediate and distal missing right inferior limb, proximal motor control, intermediate, low distal, MRC score 2/5 lower limbs, low muscle tone lower limbs with hypotonia, right Achilles tendon hyperreflexivity, live bilateral patellar ROT, hypo-aesthesia bilateral pelvic limbs, hypo-aesthesia of the lower abdomen, no sphincter disorders, positive paresis tests for the right lower limb;
- Severe global motor deficit severe lower right limb, moderate motor deficit lower left limb;
- Possible transfers assisted from the supine position to the elongated seat, from the elongated sitting position to the shortened seat;
- Possible verticalization assisted by maintaining orthostatism with lateral support;
- Possible walking with human assistance or in support of the walking frame.

The patient is evaluated functionally using specific functional scales: ADL (5p), IADL (could not be calculated because the patient did not perform current activities during hospitalization), Barthel (50p), FIM (motor score-15 / 28: average functional impotence, cognitive score- 14/14, total FIM score 29/42-average functional impotence).

Standard phosphocalcic metabolism tests were performed to support the differential diagnosis. The patient has a severe vitamin D deficiency, with very low values of 25 hydroxy vitamin D (6.8 ng / ml), the laboratory where the blood samples were performed defining the vitamin D deficiency with values < 12 ng / ml, insufficient level : 12-20 ng / ml, acceptable level 20-30 ng / ml, optimal level 30-100 ng / ml, toxic level > 100 ng / ml. PTH is within normal limits, although we would have expected secondary hyperparathyroidism; this is due to the suppression of PTH by hypercalcemia of 11.7 mg% (8.7-10.4 / mg / dl). In this regard, it is recommended to repeat the calcium levels and avoid calcium administration; Instead, vitamin D (cholecalciferol 2000 IU / day) is recommended. Bone densitometry is performed with normal DXA values for the standard regions examined, which excludes a diffuse bone genetic pathology. Considering the symptomatology and the clinical picture of the patient, the following therapeutic scheme is decided:

- Magnetotherapy back plate;
- Ultrasounds bilateral Achilles tendon, 0.4 W / cm<sup>2</sup> / 4' + 4' ;
- Galvanic bath lower limb 4 cells, individual polarity for each tank, 20' with threshold intensity ;

- Toning massage lower limbs 10' ;
- Individual physiotherapy with the objectives: spine relaxation, toning lower limb muscles, coordination re-education, gait re-education.

The patient has a favorable evolution, with a significant improvement of the symptoms after the first week of treatment with the resumption of walking without support.

It is re-examined at discharge through the BARTHEL and ADL scales, obtaining 80 points, respectively 8 points, corresponding to the quasi-dependence stage.

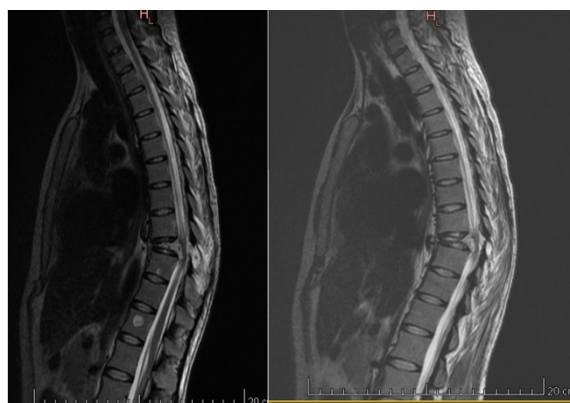
## Conclusions

Through the established early rehabilitation program, the therapeutic efficiency was significant with the improvement of clinical symptoms, as well as a marked increase in functional parameters, ensuring the patient an increased degree of autonomy and reintegration into social and family life. Pregnancy is a special situation in which vertebral hemangiomas can become clinically manifest, especially in the last 3 months of pregnancy. With the help of early physical kinetic treatment, we can significantly contribute to the rehabilitation of the remaining clinical-functional deficit, hoping for complete recovery (21).

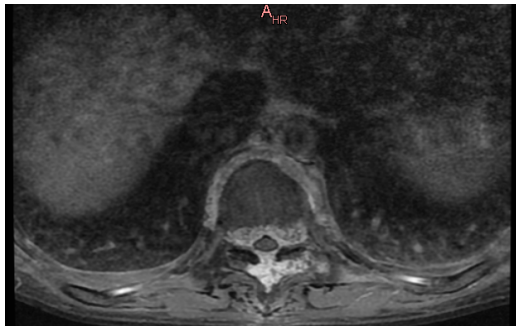
Multidisciplinary management of this case shows the importance of our comprehensive knowledge in clinical practice from rehabilitation doctors point of view (22).

**Declaration of conflict of interests.** There is no conflict of interest for any of the authors regarding this paper.

**Informed consent.** An informed consent was obtained from the patient included in the study



**Fig.1.** Sagittal CDL MRI: T9 vertebral body compression with cuneiform appearance, recoil of a bone segment at the level of the post wall, posteroinferior intracanal with compressive effect on the dural sac, focal lesion of 6/7 mm with osteolytic character at the level of 1/3 ext. and upper vertebral body T10.



**Fig.2.** CD MRI Axial section: bone structure is inhomogeneous in the T9 vertebra (body, pedicles, transverse and spinous processes, upper and lower joint processes) by the presence of predominantly osteolytic lesions, associating the visualization of bone trabeculae suggestive of hemangioma vertebral.



**Fig.3.** Slender postoperative scars healing. Posture adopted by the patient, accentuation of the dorsal kyphosis

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## Therapeutic plasma exchange in neuroimmune diseases. Rehabilitation in myasthenia gravis patients treated with apheresis procedures



WEB OF SCIENCE

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### Abstract

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique which removes large molecular weight particles, like autoantibodies, from plasma. Double filtration plasmapheresis (DFPP) is a newer technique in which plasma is not entirely removed, only the antibodies, using special filters. Myasthenia gravis (MG) is a well-known autoimmune disease characterized by antibodies against postsynaptic nicotinic acetylcholine receptors and fluctuating weakness, sometimes life-threatening. TPE is a therapeutic modality well established in MG with a positive recommendation based on strong consensus of class III evidence and in the category I of American society for apheresis. There are no adequate randomized control trial, but many cases report short-term benefit from plasma exchange in MG especially MGC. We analyzed the cases of neuroimmune disorders that were presented to our Emergency Care Unit between 2012-2020 and we concluded that good acceptance of procedure (TPE/DFPP) was observed in 72% of patients. TPE is cost-effective rapid therapy for myasthenic crisis and progressive myasthenia gravis. It reduces ICU stays and improves outcome. All in all recent studies show that the combination of rehabilitation and other forms of treatment, appropriately selected activities contribute to alleviating the symptoms of the disease, improving physical fitness, increasing muscle strength, and thus improving the quality of life.

**Keywords:** *therapeutic plasma exchange, plasmapheresis, neuroimmune disorders, rehabilitation,*

### Introduction

Rehabilitation is defined as “a set of measures that assist individuals who experience disability to achieve and maintain optimal physical, sensory, intellectual, psychological and social functioning in interaction with their environment” (World Health Organization. World Report on Disability. Geneva, Switzerland: WHO; 2011). Furthermore, an effective rehabilitation program can minimize secondary medical comorbidities, prevent or limit physical deformities, and allow the patient to integrate into society. Myasthenia gravis (MG) is a well-known autoimmune disease characterized by antibodies against postsynaptic nicotinic acetylcholine receptors and fluctuating weakness, sometimes life-threatening. MG has annual incidence of approximately 30 new cases per million, approximately 15–20% of these patients will go into myasthenia gravis crisis (MGC) and 3–8% of all patients who go into MGC will die from this condition (1). Therapeutic Plasma Exchange (TPE) is accepted by the American Society for Apheresis as first line treatment for some severe neuroimmune disorders. TPE is a therapeutic modality well established in MG with a positive recommendation based on strong consensus of class III evidence and in the category I of American society for apheresis. It can be as well used for other pathologies being

very often used for patients that suffer from Guillain-Barre Syndrome, Myasthenia Gravis as it will be highlighted further and sometimes Multiple Sclerosis (1). The exact mechanism by which apheresis treatment works in multiple sclerosis is actually not fully understood. MS patients may benefit by the immediate removal of plasma antibodies, immune complexes and cytokines. Besides effects on humoral immune system, experimental data suggest a reduction of circulating autoantigens and regulatory proteins and induction of a higher relative quantity of Treg to Th17 cells (2). Th17 is known to transfer immune and inflammatory processes through the BBB using different mechanisms: penetrating the BBB, inducing neuronal death and recruiting other CD4+ lymphocytes, thus promoting further CNS inflammation, which can lead to disease worsening and exacerbations. This made clear that Th17 cells are implicated in early MS pathology and that plasmapheresis should be taken into consideration as an effective treatment (2).

### 2. Materials and methods. Results.

Firstly, we would like to present the experience of our centre in therapeutic plasma exchange. We started using



therapeutic plasma exchange (TPE) and double filtration plasmapheresis (DFPP) in 2012 (Fig 1).

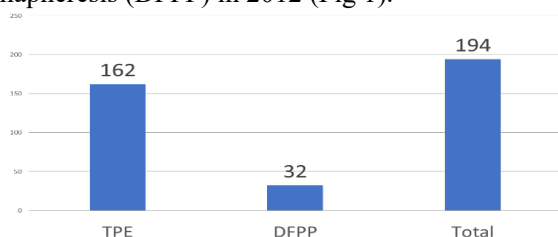


Figure 1 –number of TPE and DFPP since 2012

Since then 68 patients benefited from this procedures. Out of them 42 were patients that suffered from neuroimmune diseases, 10 being diagnosed with Miyasthenia Gravis (Fig 2).

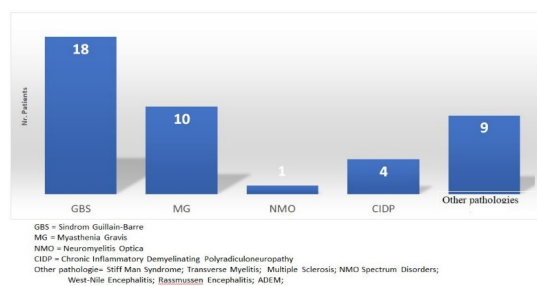


Figure 2 – patients with neuroimmune pathologies that underwent TPE/DFPP

All the patients that were treated with one of these procedures were admitted in ICU until the procedures were over. The right or left internal jugular vein was catheterized with a 20 F double lumen catheter, this procedure being performed under local anesthesia, with an aseptic technique. X-ray control is always performed to assure proper position of the catheter. For both techniques (TPE, DFFP) we used the HF440 machine (Infomed SA, Geneva-Switzerland). Cascadefiltration is a 2 steps process during which plasma is first extracted from the blood and then circulated through a second filter, the plasmafractionator. Having a membrane pore size approximately 10 folds smaller than a plasmafilter, the plasma fractionator retains larger molecules such as IgG, LDL-cholesterol and viruses.

The mean age of the patients treated with TPE was between 50-60 years (Fig 3). The adverse reactions (hypocalcemia, hyponatremia, hypokalemia, hypotension, infections, allergic dermatitis)described in the group of patients subjected to these procedures, similar to those described in the literature, were transient, completely reversible and did not require discontinuation of the procedure in the study group. The adverse reactions usually appear after the administration of albumin as replacement fluid. For example this case of GBS when after administration of first dose of albumin the patient experienced arrhythmias, marked dyspnea, hypotension (blood pressure 50/30mmHg), bradycardia (heart rate 40 beats/min), symptomatology that partially remitted under cortisone therapy and adrenaline (3). Hypotension is a rare adverse reaction, the most common side effect to TPE being hypocalcemia that appears because of chelation of calcium by sodium citrate, used as

an anticoagulant both during the procedure and in thawed fresh frozen plasma often used for replacement (4). However, we would like to highlight that most of the patients (72%) that underwent these procedures got ameliorated (Fig 4).

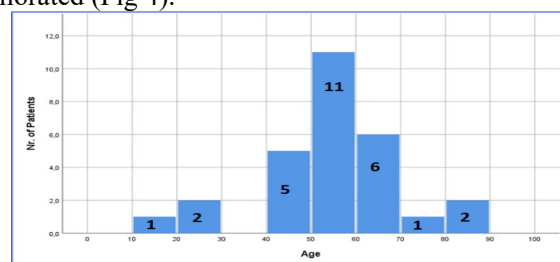


Figure 3 – median age of the patients that underwent therapeutic plasma exchange/double filtration plasmapheresis

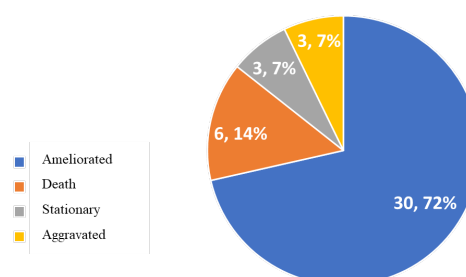


Figure 4 – clinical evolution of the patients after TPE and DFPP

Deaths (14% of patients) were not due to the procedure itself, being caused by sepsis / bronchopneumonia (Fig 5).

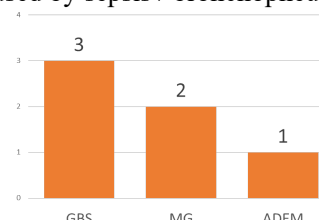


Figure 5 – number of deaths appeared after the procedures

### 3. Case Report

Plasma exchange procedures (TPE and DFPP) used by an experienced team in intensive care clinics are a safe method of treatment in severe neuroimmune diseases, therefore we would like to present the case of a 44 years old patient, known with Myasthenia GravisOssermannIIla, that was admitted to our intensive care unit for deglutition problems, extreme fatigability, breathing difficulties and dysphonia. The symptoms started 5 days prior admission into the hospital, secondary to a pulmonar infection for which she underwent antibiotic treatment.

Clinical and Neurological exam at admission revealed: very influenced state, blood pressure - 120/70 mmHg and 80 beats/minute the heart rate, she was intubated and mechanical ventilated. She had no fever and no other abnormalities at the general examination.

It is well known that therapeutic plasma exchange or IV imunoglobulins are life-saving in patients with myasthenic attacks.

Patient underwent TPE (Therapeutic Plasma Exchange) with apheresis devices on alternate days using 4% human serum albumin (HSA) and normal saline (NS) as replacement fluid. One to one-and-a-half plasma volumes were exchanged in each session with a total of 11,832 ml of patient plasma over a period of 10 days. The patient had significant improvement in her respiratory profile and was extubated. In addition, there was improvement in the overall muscle power and she was able to move without support.

We would like to emphasize the importance of plasma exchange in patients with autoimmune pathologies and the major significance of rehabilitation right after the procedure. The present case is an example of myasthenia gravis with repeated crisis attacks despite being on regular maintenance immunosuppressive therapy for the last 14 months; and, significant improvement has been seen after multiple sessions of TPE.

#### **4. Discussions**

In general, refractory cases of myasthenia gravis respond to aggressive immunosuppression and other immunosuppressive therapy including rituximab. The treatment efficacy of IVIg and TPE has been found to be equally effective with the former being preferred due to the ease of administration.

All in all, after the procedures are over, it is very important the rehabilitation of these patients. The research shows that the combination of rehabilitation and other forms of treatment, appropriately selected activities contribute to alleviating the symptoms of the disease, improving physical fitness, increasing muscle strength, and thus improving the quality of life.

#### **Physical Training**

In the prospective pilot study by Westerberg et al. (2017) (5), 10MG patients with a mild

form of the disease performed supervised aerobic and resistance training twice weekly for 12 weeks.

Physical exercise was well tolerated, and the Myasthenia Gravis Composite (MGC) score was unchanged.

Physical performance-based measures improved while muscle enzymes remained normal.

In their 2018 study, Westerberg et al. (6) evaluated functional skeletal muscle parameters in 11 MG patients, before and after conducting a 12-week supervised physical therapy regimen of aerobic and resistance strength training. After the training program, physical performance-based measures improved as well as the clinical MG composite score.

The aim of the study by Farrugia et al. (2018) (7) was to investigate whether a combination of physical and psychological therapy would help address symptoms of fatigue in ten MG patients, who have stable disease but residual problematic fatigue. There was a significant improvement in the visual analogue fatigue scale (VAFS) at the end of the program. No clear improvement was noted in the other scales. Three months later, all fatigue scores declined to baseline.

#### **Respiratory Training**

Weakening of muscles including respiratory muscles may lead to respiratory failure. Therefore, it is important to introduce the improvement of breathing exercises in the program. In available publications, the authors suggest various forms of rehabilitation - inspiratory and expiratory muscle training, breathing membrane training or endurance training. All forms of rehabilitation used bring beneficial health effects for patients, which confirms that respiratory muscle training is an important and effective element of therapy (8, 9, 10).

Aslan et al. (2014) (11) carried out an RCT investigating the effects of respiratory muscle training performed by inspiratory and expiratory threshold loading on pulmonary functions in 26 patients with slowly progressive neuromuscular disease, including MG. Maximal inspiratory and expiratory pressures and sniff nasal inspiratory pressure were improved in the experimental group when compared with the sham group ( $p < 0.05$ ). However, there was no improvement in spirometric measurements when groups were compared ( $p > 0.05$ ).

The prospective case-control study by Freitag et al. (2018) (12) investigated the effects of a sixteen-weeks respiratory muscle endurance training (RMET) on MG patients and compared the results with a control group. Eighteen patients with mild to moderate MG participated as the training group, and six patients served as controls. A modulation in the breathing pattern at rest with prolonged expiration was observed in the training group. In addition, the training group reported subjective improvements in MG symptoms, respiratory symptoms, and physical fitness. No significant changes were observed in the control group.

#### **Balance Training**

An important part of the rehabilitation process in myasthenia is balance training. Patients with MG lead a more sedentary lifestyle compared to healthy people. This affects, among other things, the reduction of bone density and, consequently, can lead to falls and fractures. During exercise, there are various physiological effects - increased skeletal muscle mass, increased number of mitochondria, which in effect improves the efficiency of neuromuscular transmission (13).

The prospective study by Wong et al. (2014) (14) aimed to determine if a 16 session workstation intervention consisting of balance strategy training (BST) could improve functional ability and balance in a group of seven individuals with MG. The quantitative myasthenia gravis score (QMG), timed up and go with cognitive task (TUG-cognitive), and foam with eyes closed (foam EC) achieved clinically significant improvements ( $>15\%$ ).

#### **Cardiac Rehabilitation in Myasthenia Gravis.**

Patients with MG are frequently discouraged from enrolling in cardiac rehabilitation by their healthcare providers or denied care at rehabilitation centers not equipped for care of such patients. Our report shows that aerobic and resistance exercise may be safe and effective for MG patients in a cardiac rehabilitation setting. Careful individualized

planning; close monitoring and frequent reassessments are warranted to ensure that the benefits of training outweighing the risks associated with exercise in MG patients (15).

The main finding of this systematic review is that there is a critical lack of high-quality evidence for the effectiveness of various rehabilitation modalities for people with MG; although a spectrum of interventions is proposed, the evidence for many of these are limited due to a paucity of robust, methodologically strong studies.

The rehabilitative approaches most frequently evaluated in the selected studies were physical and respiratory training.

Physical training, which includes aerobic, strength, and progressive resistance exercises, has proven to be an efficient strategy to improve functional outcomes (mobility, muscle strength, aerobic capacity), fatigue, physical performance, and quality of life in people with MG. The greatest benefits of physical training have been achieved in patients with a mild to moderate MG and practiced under a limited training intensity (16).

It has also been stated that general recommendations concerning physical exercise could be applied safely to patients with a well-regulated MG (16). A study even showed that long-term physical activity could reduce the autoimmune response (5). Furthermore, there was general agreement among selected studies that physical training is well tolerated by patients with MG and that the pathology does not deteriorate with physical activity (5, 10).

## 5. Conclusions

Clinically stable MG patients, just like healthy individuals, should be able to reap the benefits of physical exercise and we suggest that a reasonable program to begin with is to follow the minimum recommended international guidelines on exercise for healthy adults, i.e., at least 150 min of moderate intensity exercise a week.

As MG by its nature can involve fluctuations in symptoms dependent or independent of physical exercise, patients should always contact their physician if experiencing sustained worsening of symptoms, to receive supportive advice on further management.

TPE proved its efficacy as an emergency life-saving procedure in myasthenia crisis and is also useful as long-term maintenance therapy in patients refractory to IVIg and other immunosuppressive therapy due to its immunomodulatory effects.

## Conflict of interest

No conflict of interest for any of the authors regarding this paper.

## Informed consent

An informed consent was obtained from the patients (or the tutor of the patients) included in this article.

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## The importance of early and long-lasting medical rehabilitation in patients with brachial plexus injury



WEB OF SCIENCE

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### Abstract

**Introduction.** Brachial plexus lesions vary in severity, depending on the etiopathogenic mechanism and the level of force to which the plexus is exposed. In the same patient, several nerves of the plexus can be damaged in varying degrees of severity. Brachial plexus injuries lead to upper limb paralysis and disability. **Material and Methods.** We present the case of a 68-year-old woman diagnosed a year ago with multiple myeloma, clavicular plasmacytoma and secondary spontaneous clavicle fracture. At the same time she presented several dislocations of the shoulder and was diagnosed with brachial plexus palsy after the last dislocation. The patient was hospitalized in our department with a large motor deficit in the upper limb. A comprehensive motor rehabilitation program has been established three weeks after installing the palsy. **Results and discussion.** The evolution of the patient was favorable. It was noticed the reduction of the symptoms and slight improvement in motor deficit of the affected upper limb. The patient rehabilitation should continue for several months because the nerve regenerates slowly. **Conclusion.** In patients with brachial plexus injury, motor rehabilitation should be instituted as early as possible and continued for a longer period of time until nerve regeneration occurs. It results that early and continuous medical rehabilitation is essential in patients with brachial plexus injury.

**Keywords:** *Brachial plexus injury, shoulder dislocation, rehabilitation,*

### Introduction

Brachial plexus injury can occur through several mechanisms such as stretching, pressure, or cutting. Incomplete or complete paralysis of the upper limb results depending on the severity of the injury (1,2). The disability occurred will affect the quality of life of these patients. Regarding the causes of this condition, the most common is traffic accidents, especially motorcycle accidents. In these cases the most of the victims being young males. Other traumatic causes are worth mentioning: accidents at work, sports injuries, incised wounds, gunshot wounds, carrying a heavy rucksack and patient malpositioning during surgery. The tumors, irradiation, and congenital abnormalities such as cervical ribs can be nontraumatic causes of brachial plexus injury (3,4,5). Shoulder dislocation is a common pathology with an annual incidence of 23.9/100000 of which 85-98% are anterior dislocations. The peak incidence is in young males; however, in women, the peak age of incidence is 61-80 years (6). Nerve injuries resulting from shoulder dislocation occur rarely (13,5%) but they associate a high risk of persistent compromise of limb function (7). Neurologic injuries secondary to this condition are characterized mainly by neurapraxia and rarer axonotmesis (8). The three major mechanisms of brachial plexus injury are traction of neural structures by

the humeral head, compression of the brachial plexus exerted by the humeral head or nerve compression by haematoma and fibrous tissue (8). Clinical assessments, electrophysiologic examinations and imaging studies (standard myelography, computed tomographic myelography, and magnetic resonance imaging) are used for evaluation of the brachial plexus (5,9). The pathological condition and the location of the lesion guide the therapeutic measures. The treatment of this disease is either conservative or surgical (5,9).

### Objective

The goal is to demonstrate the need and importance of early and long-lasting medical rehabilitation in brachial plexus palsy.

### Material and methods

We present a case of brachial plexus injury that was hospitalized and treated in our Physical Medicine and Rehabilitation department for two weeks. The case presented is that of a 68-year-old woman from the urban environment. She was admitted in our department for pain and functional deficit in the right shoulder and also a significant motor deficit in the right upper limb. One year ago, our patient was diagnosed with Multiple Myeloma which was treated with chemotherapy and stem cell transplantation. Multiple myeloma was discovered



following a spontaneous clavicle fracture on the pathological bone in the context of this disease (clavicular plasmacytoma). It should be noted that the patient had several recurrent shoulder dislocations for which she was immobilized in the Dessault bandage. For the last dislocation of the shoulder, surgery was performed by fixing the humeral head with two Kirschner brooches. Our patient states that the motor deficit in the right upper limb appeared after the last shoulder dislocation. She presented for admission three weeks after the onset of paralysis. Diffuse osteoporosis and dyslipidemia are also noted in the patient's personal pathological history. Physical examination revealed: right scapular girdle muscle hypotrophy; right shoulder inferiorly subluxated 1 centimeter, with pain and stiffness on mobilization; "fallen" right hand, with the appearance of a "swan neck"; significant motor deficit in the right upper limb. Evaluation of the muscle strength using the Medical Research Council scale (MRC) highlighted motor deficit in: shoulder flexor and abductor muscles (value 1/5 MRC); elbow extensors (value 1/5 MRC) and flexors (value +3/5 MRC); fist extension (value 1/5 MRC); metacarpophalangeal extension of the fingers (value -2/5 MRC); hand supination (value 1/5 MRC); thumb abduction (value 1/5 on the MRC); finger flexion (value +3/5 MRC). Examination of deep tendon reflexes shows abolished tricipital reflex and diminished stiloradial reflex. Superficial hypoesthesia in the right C7 root territory was found.

Functional evaluation reveals: the visual analog scale (VAS) for pain intensity index = 8, the activities of daily living scale (ADL) index = 7 (assisted independence). The instrumental activities of daily living scale (IADL) index = 5/8 and the quality of life scale (QoL) index = 70, proving a moderate impairment of quality of life.

The results of radiological examinations performed pre and postoperatively at the last shoulder dislocation are presented below (Fig 1, Fig 2, Fig 3).



Fig 1. Inferior subluxation of the right scapulohumeral joint and clavicle fracture with pseudarthrosis, diffuse bone demineralization



Fig 2. The condition of the joint after stabilizing the subluxation of the shoulder with 2 Kirschner brooches



Fig 3. Reduction of dislocation in the control radiography.

Electrodiagnostic studies reveals severe axonal degeneration of the right radial and axillary nerves (Fig 4).

Summary EMG data													
Motor CV													
Test	Stimulation site	Lat, ms	Ampl, mV	Dur, ms	Area, mV×ms	Stim, mA	Stim, ms	Dist, mm	Time, ms	Vel, m/s	Vel, norm, m/s	Vel, dev, %	
<b>R. Deltoides, Axillaris, C5 C6</b>													
8	Erb's point	2.4	0.09	7.8	0.43	21	0.5	170					
<b>R. Extensor indicis, Radialis, c6 C7 C8</b>													
3	axilla	6.4	0.9	6.6	2.6	28	0.5	60					
<b>R. Abductor digiti minimi, Ulnaris, C8 T1</b>													
2	wrist	2.1	5.7	5.5	16.8	25	0.2	70					
	elbow	6.5	5.0	6.35	15.7	25	0.2	180	4.45	40.4	60.0	-32.6	
	arm	7.4	4.2	6.8	14.3	27	0.5	100	0.85	118	60.0	+96.1	
<b>R. Abductor pollicis brevis, Medianus, C8 T1</b>													
1	wrist	7.2	2.8	8.66	13.4	40	0.2	80					
	elbow	11.2	2.5	9.86	13.0	40	0.2	200	3.99	50.1	60.0	(N)	
Sensory CV													
Test	Site	Lat, ms	Ampl, $\mu$ V	Dur, ms	Area, nV×s	Stim, mA	Stim, ms	Dist, mm	Time, ms	Vel, m/s	Vel, norm, m/s	Vel, dev, %	
<b>R. Ramus superficialis n. radialis, C5 C6</b>													
7	Middle third of forearm		0			22	0.1						

Fig4. Impairment on electromyography of the right radial and axillary nerve.

## Results

The objectives of the rehabilitation program in this case are: pain relief, maintaining/restoring the mobility of the joints, maintaining muscle trophicity and preventing the atrophy of the denervated muscles, prevention and treatment of vasculotrophic phenomena, motor and sensitive rehabilitation of the affected upper limb, training of ADLs, increase in bone mineral density.

In our department, the patient followed pharmacological treatment consisted of analgesics, neurotrophic drugs and antiosteoporotic drugs/bone-strengthening drugs. The medical rehabilitation program was applied twice a day and consisted in analgesic electrotherapy, electrical stimulation on the denervated muscle groups, kinetotherapy, mirror therapy, occupational therapy. It was also used orthosis for fist and fingers posture of the right hand. The patient was also recommended to wear a scarf to avoid subluxation of the humeral head with ligamento-capsular distension. It should be mentioned that the motor rehabilitation was not initiated until three weeks after the installation of the motor deficit. The evolution of the patient was favorable regarding the improvement of the symptoms (admission index= 8 / discharge index= 4 on the visual analogue scale). But the evaluation of the muscle strength at discharge shows a slight improvement of the motor deficit of the affected upper limb. This fact can be attributed to slow nerve regeneration and to the late presentation in our service three weeks after the installation of motor deficit.

## Discussion.

In our case the injury of the brachial plexus was determined by the clavicle fracture complicated with pseudarthrosis and recurrent dislocations of the shoulder. In this situation, several possible mechanisms can be discussed: stretching of the brachial plexus by recurrent shoulder dislocation or compression exerted by the humeral head. Our patient would have needed magnetic resonance imaging, this investigation being valuable in the evaluation of the brachial plexus (10).

The results of several clinical studies have shown that in addition to the deficiency of sex hormones, dyslipidemia promotes the development of osteoporosis in both women and men (11,12). In our patient menopause and dyslipidemia can be considered predisposing factors for osteoporosis. In this case neglected osteoporosis can adversely affect the evolution of the clavicular fracture and can cause other fractures. Instead antiosteoporotic treatment with bisphosphonates can lead to a favorable evolution of the case.

Furthermore the patient's advanced age represent an additional risk factor. According to the specialized literature one of the major risk factors for neurologic complications of shoulder dislocation is considered to be the age above 50 years old (8). The risk of nerve deficit secondary to shoulder dislocation is higher in case of low-energy trauma as shown in some studies (7,8). In reference to our patient, the dislocation occurred in the absence of any significant trauma. Regarding the affected nerves, studies have shown that the axillary nerve is the most commonly one to be injured in scapulohumeral dislocation (with a 100% rate in some studies). In addition, multiple nerve injuries were more often than mononeuropathy. Complex neurologic deficits were found in association with older age, female sex and low-energy trauma (7). In our case, the electrodiagnostic studies examination performed on the 68 years old female patient showed multiple nerves injuries including the axillary nerve.

A study stated that the majority of neural complications have been observed after the first time than after recurrent scapulohumeral dislocations (13). On the contrary, our female patient presented motor deficit after a recurrent shoulder dislocation.

The main goals in the rehabilitation of brachial plexus injury are pain suppression, recovery of somato-sensory deficits, prevention of muscle atrophy, prevention of secondary deformities. Neuropathic pain can be an obstacle in the recovery of patients with this condition. Pharmacotherapy is frequently used to control neurological pain. International guidelines recommend as a first line treatment anticonvulsants such as gabapentin or pregabalin and tricyclic antidepressants. Our patient received 600 milligrams of gabapentin per day. In case of postganglionic lesions or when some fibers are preserved, Transcutaneous electrical nerve stimulation (TENS) can be used as analgesic therapy (14). Kinetic exercises helps restoring the deficits caused by the disease. Passive muscle stretching and electrostimulation of the denervated muscles are useful in preventing or limiting the development of muscle atrophy (14). These means were applied to our patient.

Medical rehabilitation has a very important role in the management of brachial plexus injury and should be started as early as possible after installing the motor

deficit to prevent irreversible tissue changes such as muscle atrophy (15). Also motor rehabilitation requires longer time due to slow nerve regeneration at a rate of approximately 1-3 mm/day. Mirror therapy is an important rehabilitation treatment method. It is very efficient in the neurological fields and also in hand rehabilitation. The brain can be trained to relearn some movements through the help of the mirror. The general method of practicing this therapy initially involves explaining it to the patient and his/her agreement on it. The patient sits at a table with his/her hands on it. It is important that the hands do not have clothes or jewelry on. In front of him, on the table, is placed a mirror across the midline of his/her body. In front of the mirror the patient places the hand without motor deficit and behind the mirror he/she puts the hand with motor deficit. The patient's attention and visual axis are concentrated in front of the mirror to the movements of the healthy hand. This induces an optical illusion and the patient has the impression that he/she performs those movements with the motor deficit hand, so the brain transmits signals to the affected hand and can initiate those movements. Mirror therapy should be stopped immediately if the pain increases on the injured side (16). Our patient performed this type of revolutionary therapy achieving good results. In our patient, medical rehabilitation played a very important role not only in regard to the neuromotor outcome, but also in some psychological aspects. A study from 2018 relates that brachial plexus injury can significantly influence psychological well-being, resulting in conditions such as posttraumatic stress disorder, depression which further interfere with the physical rehabilitation outcome (17). However, our patient stated that she felt progress after the first few medical rehabilitation treatment sessions which improved her motivation, treatment engagement and the neuromotor outcome.

### Conclusions

The peculiarity of the presented case is that the brachial plexus palsy occurred as a result of a recurrent dislocation of the shoulder and a spontaneous clavicular fracture on the background of a monoclonal gammopathy and clavicular plasmacytoma. Motor rehabilitation followed by the patient led to a slight improvement in motor deficit but its continuation is necessary to achieve optimal results.

It can be concluded that brachial plexus injury requires early, sustained, and long-lasting motor rehabilitation.

### Conflict of interest

There is no conflict of interest for any of the authors regarding this article.

### Informed consent

In this article was included an informed consent that was obtained from the patient.

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