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Homonymous hemianopsia versus unilateral spatial neglect rehabilitation strategies in stroke patients

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Abstract

Visual rehabilitation therapy is one of the most problematic issue in stroke rehabilitation. The difficulties consist in specific assessment of visual deficit and poor results reports by the authors of the clinical studies. Opposite, experimental studies reports encouraging results that give hopes in this specific rehabilitation therapy. There are still difficult to analyze different aquisitions concerning various visual residual deficits after stroke, the main rehabilitation targgets being motor rehabilitation in order to ensure at least a partial autonomy in day by day life. All the studies that proved there are chances for a better quality of life if there is an improvement of visual abilities together with motor and cognitive skills with a better rehabilitation prognosis. The aim of this paper is to make a brief report regarding two of the most important visual deficits after stroke as are homonymous hemianopsia and neglect. Starting with differential diagnosis, neuroplasticity and specific rehabilitation available method, the main issues are discussed. a better understanding of phenomena that are associated with spontaneous rehabilitation, or enhancing the progress of recuperation by various method, could be able to bring a new light and hopefully better results in rehabilitation for these patients

Key words: *stroke, visual impairment, visual rehabilitation, neuroplasticity, homonymous hemianopsia*,

Introduction

Homonymous hemianopsia (HH) is one of the most common disorders following ischemic stroke, usually associated with post-chiasmatic lesions, which has serious impact on motor rehabilitation, visual skills, driving, reading, and self-care activities (1). Transitive hemianopsia that are followed by spontaneous recovery can be associated with high levels of glycemia or hypertension and with other neurological conditions as are transient ischemic attack, migraine, occipital, parietal or temporal seizures, hemorrhagic stroke, brain tumors or trauma, demyelination process, antiphospholipidic syndrome, central nervous system infections or Alzheimer's disease (2-7). An important step in recognising hemianopsia is the differential diagnosis with hemineglect disorders that can both followed after stroke onset. For this differential diagnosis there is needed to take in consideration some important elements as are: subjective complaint of the patients, aetiology and localisation of the lesion, extension of the visual deficit by clinical examination, specific visual field testing techniques for diagnosis of visual blindness (scotoma) or other types of visual field defects (8). The perimetry results depends on patient attention and understanding the tasks, fixation maintaining ability, and the examination accuracy. automated perimetry, most used in clinical practice can offer important information useful for differential diagnosis (9). Improvement of HH after stroke can constitute a serious challenge with an impact on entire rehabilitation strategies and results, especially in ischemic stroke patients. Despite the fact of high reported prevalence of visual disabilities associated with stroke (approximately one third of patients present visual disorders after stroke), the visual rehabilitation therapy is inconsistent and has no precise milestones that can constitute a real protocol in stroke rehabilitation therapies schema (10). Moreover, visual field deficits is relatively undervalued in the clinical setting due to poor prognosis and imprecise results after different rehabilitation methods (11). HH persistence is a negative predictor for patients outcome despite the motor and speech rehabilitation therapies efforts (12). It is possible that adding a systematic vision rehabilitation to other methods for stroke rehabilitation could consistently improve patient's quality of life (13, 14).

Many strategies that already developed in this research field of HH rehabilitation met scepticism in

scientifically communities, therefore, clinical approaching was not constant followed, and there is no consensus regarding the methods and therapies applied in this form of visual disabilities. There are also only few studies regarding different methods applied for HH rehabilitation with various approaching that have a common technique of repetitive exercises of a special visual task that can hopefully stimulate the visual spared abilities in order to reach a performance that can be useful in improving day by day activities (12). Unfortunately, during these therapies, patients expectations are high, and they are followed by a decline after their hopes are not accomplished (15, 16). Despite of these concepts there are reports that showed that visual field defects can be partially reparable and certain degrees of deficiencies can be improved (17, 18). Improving HH together with motor skill, based on various strategies, can constitute a serious background for developing more detailed rehabilitation strategies that could lead to and partially or even total indepented life in stroke patients (15, 19). Patient who suffered an acquired visual disability as is hemianopsia have to make dramatic behavioural and compensatory adjustments in order to trying to keep their independence in a world strongly relied on visual stimuli. Understanding the function of the visual system in and neuroplasticity phenomena can be an important step toward a better rehabilitation of these patients, improving their outcome chances, and finally their life quality.

Unilateral spatial neglect (USN) consist in unresponsiveness to any visual or tactile stimulus on one side of the body (contralateral side defect), that cannot be attributed to sensory or motor deficit (20). This condition is associated with lesions in the right hemisphere, particularly in the right hemisphere (inferior parietal lobe, superior temporal gyrus and/or inferior frontal gyrus) and with poor prognosis (21). There was reported that approximately 85% of the patients with subacute or acute ischemic lesions associated with stroke, presents variable grades of USN, and there is no universal agreement concerning the assessment methods for USN evaluation (22). Topographical evaluation of the lesions showed that neglect was more common and severe in posterior associated cortical lesions, and behavioural assessment as is automatic right side orientation was the most sensitive clinical estimation of USN (22).

Clinical presentation of the patient is leading to a confusion with HH at the first evaluation of the patient, but a detailed observation of the patient concerning spatial orientation is concluding to a correct diagnosis. The automatic tendency orientation toward the right side of their environmental space, in the presence of a visual stimuli constitute a strong indicator of USN. The role of gaze direction in USN seems to be a particular mechanism used by the patient in order to adapt to USN (23). The gaze can be processed despite the fact the patient is unable to attend to it, being attributable to residual abilities in sensorial processing function that can modulate attention toward the left side of the environmental space (24). Despite the fact the initial evaluation can be interpreted as an artefact associated with clinical presentation of the patient due to ischemic lesions, a careful clinical and imagistic evaluation may conclude to a correct diagnosis of USN. The grade of spatial perception can be also variable, according with the possibility to partially compensate the defect by residual functions. If the damage produced by ischemia is large and a cystic region is forming in the place of ischemic tissue (where the neuronal death was produced) as the consequence of stroke, the rehabilitation process is expected to be very poor (25). The aim of this paper is to emphasize the main rehabilitation techniques in HH and USN rehabilitation, based on physiological support of visual system in brain circuitries, on plasticity and reorganisation proprieties of neuronal networks and on individual patients abilities to improve their conditions, according with cognition, age and stroke features.

Ethiopathogenesis and functional impact

The main ethiopatogenetic factors associated with HH are represented by ischemic stroke, mainly associated with brain lesions in posteriors cerebral artery territories and middle cerebral artery territories (26), but can be also associated with traumatic brain injury or brain tumors and cerebral infectious disorders (27). Moreover, the visual field defect it is associated with motor, sensory, cognitive deficits and/or aphasia or depression. All of these disabilities contribute alone and together to a serious impairment of life quality, constituting an vicious circle, that consist in aggravation one each other, and being, in this way, difficult to improve. After an ischemic stroke, motor deficit can be serious negatively influenced by visual disabilities (Barthel index that measure the performance in activities of daily living decreasing when visual disabilities are associated),

quality of life being more affected in young patients than in older ones (28). High dependency in day by day activities and depression that are persistent at 3 years after stroke onset, are factor that have a major contribution to a low quality of life in stroke survivors (29). The mood and emotional disturbances may be treated or prevented by improving of rehabilitation progress (regarding motor/sensorial/visual disabilities) in a period of 1-2 years after stroke onset decreasing the stressor factors in stroke survivors and essentially contributing to the quality of life (30). Neglect it is mainly a consequence of disrupted internalized representation of the environment perception with associated cortical and white-matter tracts dysfunction having as a consequence an inter-hemispheric lack of communication and manifested as neglect in clinical assessment (most used test for clinical assessment test are Catherine Bergego scale, line bisection test and star cancellation test) (31).

Neuronal plasticity and reorganisation of neuronal networks

In general, spontaneous improvement of HH occurs in about 50% of stroke survivors, in the first 1-3 month after injury (32). After 6 months spontaneous recovery need to be interpreted with prudence because significantly improvement is improbable (32). Spontaneous recovery is based on a cascade of event that follow after ischemia onset and consists in molecular, cellular and electrophysiological changes which will enhance neuronal recovery. All of these phenomena are triggering cortical reorganisation and regeneration being the background of functional neuronal recovery. Experimental studies showed that these events begin very early, in few hours after stroke onset, reaching a peak in 7-14 days and being nearly complete in approximately 30 days. Evidence from animal studies shows that after ischemic injury, a cascade of genetic, molecular, cellular, and electrophysiological events is triggered which promote neural recovery. Together, these events drive cortical reorganization and regeneration, and provide the neural substrate for spontaneous recovery. In rodent models, these events begin within hours after stroke, peak at 7–14 days, and are nearly complete at 30 days (33). Recovery continue in the next month but more slowly, therefore became important to accelerate and improve recovery in the first 30 days after stroke (34, 35). There are various difficulties in clinical practice to realize this goal due to instability of some patients in the first 14 days after stroke. In the meaning time there are reports that sustain that active rehabilitation in the first 24 h is dangerous and can be harmful (36). One of the mechanism associated to recovery after stroke consists in axonal sprouting in cortical areas adjacent to infarct being detectable with anatomical mapping of cortical circuits (demonstrated by immunohistochemical staining patterns of axonal proteins, such as neurofilaments or synapse-associated proteins) one month after the stroke but the signal that initiates axonal sprouting is not known (37, 38). After the recovery reach the point where from the acquisitions are very slow, the patients can concomitant develop a deformed perception of the visual field (spherical deformation of the objects at the edge of the blind visual field). The hypothesis enhanced was that cortical reorganization can occur in the human adult visual system after loss of cortical input as a consequence of cortical reorganization (39). There are several reports that sustain that the V1 area has the possibility to exert plasticity phenomena and thus to recuperate, at least partially, functionality (40, 41). The same process is taking place in old patients that present an age related macular degeneration develop a large scale reorganisation of visual cortex after deafferentation due to the lack of visual stimuli that can arrive at visual cortex and (42). There is unreported evolution of the patients where the homonymous hemyanopsia is superimposed on a retina with age related macular degeneration. Anyhow, multiple causes that can affect the visual perception (ophthalmological causes and neurological causes), when are present in the same patient, can decrease considerable the rehabilitation outcome and can constitute together a poor prognosis for targeting an independent day by day life. Stroke recovery is based on the new system of neuronal connections or on the functional properties of neurons in a recovering area (43). Regarding the USN rehabilitation, the functional outcome depends on neglect type: personal, peripersonal and extrapersonal. Spaccavento at all reported that there are very variable rehabilitation grades of patients with neglect (that can have differed in motor and cognitive deficits at admission and discharge) according with the patient's age and lesion extension (44).

Methods for homonymous hemianopsia rehabilitation

Current knowledge offer four main strategies for HH rehabilitation: replacing partially the damaged visual field with intact visual field by prisms (optical therapy), partially restoring the lost visual field

(restorative therapy), stimulating detection capacities in blind visual field (stimulation therapy) and reorganisation of visual function by eye movements in order to enlarge the cortical regions for visual perception (compensatory therapy) (12, 45).

1. Optical therapy - consists in applying optical devices that can deviate the blind visual field toward the functional intact visual field, offering to the patient a correction with prismatic lenses. A high power prismatic lens (30-40 dioptre) is orientated towards the hemianoptic field, at about the level of the limbum (46). By peripheral location of the prism will lead to peripheral exotropia that will put the object from blind field into the normal functional field, enlarging the degrees of perception in blind field with about 20 degrees (47). Lower dioptre (D) prismatic lenses as are those below 20 D can only provide about 10 degrees of enlargement for blind visual field (48). The long term success rate of optic therapy applying, with prismatic lenses correction, is very variable as is reported by Bowers at all (27 – 81%) from very low to good compliance (47). The main reasons for low compliance were the anxiety of the patients due to sudden visibility of some objects in the visual field, and consequently, confusion and anxiety (47). Other objections that decrease the compliance are difficulties to reading with this optical correction (very often due to necessity of bifocal correction), difficulties to step on descending stairs (may produce diplopia) (47). There is also important to take in consideration the costs for Fresnel prisms that are used as a permanent correction in optical therapy for homonymous hemianopsia (49). There are also patients that can have a good toleration of prismatic lens correction that means that are already used to wear and they don't need to change the head position and posture of the body, in order to get a better image of the environmental visual field. There is a study that reported that approximately 15-17% of the patients do not meet the criteria for prismatic lens correction, due to low tolerance (withdrew in the first week) or due to the reason they were not eligible ; the rest of participants in Bowers at al study confirmed that prism correction helped them to avoid obstacles during mobilisation (47). Monoocular prism correction should be taken in consideration for the patients who present age related macular degeneration in an advanced stage (50). Based on acceptance of these devices (Fresnel prism) optical correction of visual field defect can constitute a modality to reduce the patients visual discomfort during the rehabilitation process. There are needed more studies to prove the reliability and efficacy of prismatic correction for these patients due to multiple disabilities that they presenting at the time of the admission into the hospital, that can constitute a serious burden from physical and psychological point of view. Anyhow, this treatment can bring a hope for improving patient condition during the rehabilitation therapy, being one of the reachable improvement of functionality in stroke patients.

2. Restorative therapy - is based also on the brain plasticity and on its ability for reorganisation after an injury. Training the patient to perceive the light at the limits between blind visual field and healthy visual field an enlargement of 5 degrees can be obtained (8). The stimulation of the border zone between blind visual field and healthy visual field can lead to neuronal plasticity and neuronal network reorganisation but the proves in this direction are inconsistent. The difficulties to objectify this theory are based on different devices for visual field assessment in clinical trials and inconsistent results (12). Therefore visual restoration therapy remains controversial and the scientific community has a high grade of scepticism regarding its results.

3. Stimulation therapy - consists in stimulation of existing visual capacities in blind visual field by training the patients to detect visual stimuli targeted on the spared area in the blind visual field. The stimulus consists usually in a flickering light that has to be detected by the patients. After one year of intensive training some authors reported the ability of the patients to identify the lightening stimuli and, in the same time, an expansion of visual field of 20 degrees (46). There are sceptic approaching of these results due to lack of indication of the topography of the lesion during these reports, and due to lack of evidences of brain plasticity that can support the findings. More studies are needed to transpose the animal studies that proved brain plasticity due to visual rehabilitation process to the human subjects, therefore at the moment are interpreted as speculative (51, 12).

4.Compensatory therapy - saccades (alone or with auditory stimulus together) - consists in training the patients daily during a long period of time. The method consists in training the patient's to perform saccades in the blind field, in order to enlarge the area of perception, together with enhancing the spatial organisation of ocular movement toward the hemianoptic field, by increasing the number of

fixations toward the visual field (usually the method consist in stimulation of flashing stimuli vision) (12). The basis of this visual achievement is changing the brain activity by activation of striate and extra-striate cortex and increasing their performances (12).

Methods for unilateral spatial neglect rehabilitation

The interest for unilateral spatial neglect rehabilitation is specially directed toward rehabilitation of left spatial neglect after ischemic stroke in right hemisphere, which is more common and more often associated with left hemisphere stroke (52). The techniques are variable and consists mainly in different approaching. One of the technique is based on the stimulation of gaze direction toward left using top-down stimuli that are variable in intensity, number or duration for about 20 hours of training due to 20 days (53). Other rehabilitation methods are using ascending sensory stimulations as are vestibular stimulations, optokinetic stimulations and electrical stimulation of the neck muscles with good results (54). A new and promising methods for unilateral spatial neglect rehabilitation consist in transcranial magnetic stimulation and transcranial direct current stimulation that are non invasive technique with encouraging results (55). The fundamental theory that is the basis of these method consist in creating a competition between left and right hemisphere with enhancing the activity of right hemisphere in order to reduce the unilateral spatial neglect in right hemisphere lesions (56).

Future perspectives

Despite the fact the methods regarding homonymous hemianopsia and unilateral spatial neglect rehabilitation are different, they have one common concept as is stimulation of cortical residual functions for new perception in order to reduce the blind deficit in visual field. This concept is based on neuroplasticity of neuronal network that prove the learning process of the brain can be continued in adulthood and can constitute a starting point for various abilities rehabilitation that disappeared after lesions. There are needed more clinical studies in order to organize the methods proved to be efficient in this patients in order to establish a clinical valuable protocol. Novel techniques as are transcranial magnetic stimulation and transcranial direct current stimulation could bring a new hope for the patients who suffer from these deficits that could impair seriously their entire rehabilitation progress.

Conclusions

Further development of these strategies, based on experimental and clinical studies are needed. Interdisciplinary team that is specialized on different types of training for patient rehabilitation needs to collaborate for the best results. All the data reported are promising and their implementation and future development can significantly improve the quality of life for stroke patients survivors.

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Our experience regarding rehabilitative, orthopedic integrative interdisciplinary approach in patients with disabling neurological posttraumatic sequelae. Case series and some related literature pointing

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Abstract

Introduction Traumatic brain injury (TBI) and / or spinal cord injury (SCI) usually occur in a polytraumatic context, and may produce catastrophic central nervous system (CNS) damages and secondarily extensive dysfunctional biomechanical alterations. This study aims to illustrate the interdisciplinary collaboration between neurorehabilitation and orthopedic clinics in our hospital, focusing on the results of surgical interventions intended to correct the fixed-flexion deformity of knees, in patients with disabling sequelae after CNS severe lesions.

Material and methods Between 2005-2018, in the Neuromuscular Rehabilitation Clinic of Teaching Emergency Hospital "Bagdasar-Arseni", 13 young patients (mean age 37.4 +/- 12.6; median 31; limits 26-43) with multiple articular stiffness and joint deposturing sequelae after severe CNS trauma have been transferred from other medical units. Twelve had bilateral knee flexion contractures, two associated additional elbow stiffness, and in three patients ectopic ossifications of the hips, with ankylosis in extension or painful flexion were found. Patients were subsequently transferred for iterative orthopedic interventions: hamstring lengthening (pes anserinus and femoral biceps tendon transpositions) in 12 cases, associated with posterior knee capsulotomy, traction and/or resection of neurogenic heterotopic ossification around the knee or hip joints and casting in 8 of them.

All orthopedic interventions were followed by progressive rehabilitation programs. Spasticity was assessed with modified Ashworth scale (mAS). In pre-/ and post orthopedic surgery, all patients were assessed using an adaptation for adults of the Gross Motor Function Classification Scale, Expanded and Revised (GMFCS – E&R).

Results Twelve patients had knee joint stiffness and chronic flexion contracture: 77% were severely limited in their walking ability, depending on wheelchair (GMFCS – E&R level IV), respectively 23% were bedridden, non-ambulate and totally dependent in all aspects of care (GMFCS – E&R level V).

Knee orthopedic serial interventions were followed by iterative, individualized rehabilitation treatments, and 50% subjects have regain their capacity to walk independently (GMFCS – E&R level II), respectively 50% succeeded to walked with assistive devices (GMFCS – E&R level III).

Discussion Both neuro-muscular system deficits and joint disorders can produce locomotor system abnormalities, joint complications and limb dysfunctional problems. These disturbances represent targets and therapeutic objectives for rehabilitation. Chronic knee flexion contracture, stiff elbows and/or hips, periarticular neurogenic heterotopic ossification: all represents major challenges in the complex management of patients with sequelae after CNS severe traumatic events.

Posterior capsulotomy addressed to a stiffed, distorted knee joint, corrects the limb axis and expands the range of motion (through the angle gained by the eliminated flexion contracture), and sometimes restores the patient's ability to walk. Serial orthopedic interventions, followed by sustained postoperative rehabilitation, had a decisive influence on obtaining good functional results.

Conclusions Comprehensive, multiprofessional approach and collaboration between neurorehabilitation and orthopedic teams are essential for the therapeutic management of patients with severe contractures post neuraxial lesions.

Proper evaluation and goal setting are mandatory for rehabilitative management, pre-/ and post orthopedic corrective surgery. Harmonized timing for iterative interventions, followed by postoperative structured, sustained (often for life-time) rehabilitation are essential for obtaining functional results. Adequate prophylaxis of complications represents a main therapeutic objective, as well.

Key words: *traumatic brain injury (TBI), spinal cord injury (SCI), vegetative status, spasticity, contracture, capsulotomy, orthopaedic surgery, neurorehabilitation*

Introduction

Traumatic brain injury (TBI) and / or spinal cord injury (SCI) usually occur in a polytraumatic context, and may produce catastrophic central nervous system (CNS) damages, with secondarily extensive dysfunctional biomechanical alterations (**1-3**).

This study aims to illustrate the interdisciplinary collaboration between neurorehabilitation and orthopedic clinics in our hospital, focusing on the results of surgical interventions aimed to correct the fixed-flexion deformity of knees, in patients with disabling sequels after CNS severe lesions, and respectively, the consequent facilitated progress reached in their complex rehabilitative approach.

Orthopedic surgeons are treating the secondary effects of neurologic lesions, as expressed in articular and periarticular tissues dysfunctions. Orthopedic surgery and neurorehabilitation interventions have common goals: relief of pain, prevent and adjust deformities and joint dislocations, preservation and recovery of function. Maintenance of multilevel joint balance is essential for efficient standing and sitting.

Knee flexion contracture is one of the most common complications in CNS lesions, irrespective its etiology: vascular, traumatic, infectious, neoplastic, etc. Causes of knee contracture lie in hamstring spasticity, hip flexion contracture, gastrocnemius and soleus muscle tightness, and posterior knee capsule stiffness.

Orthopedic management should be assessed to the correction of rotational deformities, lengthening of shortened muscles, or shortening the elongated ones, correction of joint contractures, followed by sustained rehabilitation – orthoses and physical-kinesiological therapy. Hamstring lengthening might be sufficient for the correction of knee flexed contracture; if associated with posterior capsulotomy it prevents recurrences (4).

Treatment should reduce (as possible) disability and facilitate mobility toward patient`s independence.

Material and methods Between 2005-2018, in the Neuromuscular Rehabilitation Clinic of Teaching Emergency Hospital "Bagdasar-Arseni", 13 young patients (mean age 37.4 +/- 12.6; median 31; limits 26-43) with multiple articular stiffness and joint deposturing sequels after severe CNS trauma have been transferred, from other medical units.

Demographics, medical history, neurologic and orthopedic diagnosis were recorded. Patients and/ or their kin expressed their agreement to be photographed for academic purpose. Data anonymization and careful removing personally identifiable information were performed. Ethics approval of the study was obtained from our hospital's Bioethics Commission.

Twelve subjects had severe knee joint stiffness and bilateral chronic flexion contracture; average preoperative knee flexion contracture was 95.5^{0} (range 60^{0} to 120^{0}).

Besides knee joint stiffness, ectopic ossifications of the hip with ankylosis in extension or painful flexion was found in three of them, and in two subjects additional elbow stiffness (90^{0} flexion).

Previously to admission in our department, all patients had inefficient preventive procedures, unsuccessful physical therapy and bracing. All were nonambulatory because of the catastrophic CNS sequelae lesions and /or joint contractures.

Patients were carefully evaluated by a multidisciplinary team, who assessed the general health status, foregoing to decide a specific orthopedic intervention. All patients had a stabile clinical condition, neither pulmonary nor urinary infections, and no pressure sores.

Prior to the goniometric articular evaluation, modified Ashworth scale – mAS (5) was used to evaluate resistance during passive soft-tissue stretching, applied throughout the entire (possible) range of motion (ROM). All patients were quoted 4 on mAS (segmental rigidity, in flexion/ extension, abduction/ adduction), passive movement being not possible. Preoperative total ROM was measured in all patients. All patients were evaluated and submitted a daily program of passive extension-flexion movements, aimed to improve ROM amplitude, prior to the orthopedic intervention (-s).

Pre-/ and post orthopedic surgery global functional status of the patients was assessed using a corresponding for adults adaptation (we have made) of the GMFCS – E&R (6), because it was useful and easier to apply than other evaluation tools (Tegner Lysholm knee score (7) and/or other scales (8). Table I summarizes the general criteria for sample selection, description and case stratification with GMFCS – E&R scale.

Surgical Techniques Different orthopedic techniques were used to correct the severe dys-

posturings: teno-muscular transpositions, capsulotomies, arthrolysis, heterotopic ossification excision surgery of the hip or knee joints.

Table I. Adapted GMFCS (– E&R) general criteria for cases stratification

	General headings for each level	
Level **I**	Walks without limitation	Near normal gross motor function, walks independently
Level **II**	Walks with limitations	Walks independently, but has difficulty with uneven surfaces; minimal ability to jump
Level **III**	Walks using hand-held mobility device(s)	Walks using assistive devices: canes, crutches, anterior or posterior walkers; "may require a seat belt for pelvic alignment and balance. Sit-to-stand and floor-to-stand transfers require physical assistance from a person or support surface"[6]
Level **IV**	Severely limited self-mobility. The mobility is based on the wheelchair. Subject can use powered mobility	Might use powered mobility (a scooter or other type of powered mobility device controlled with the joystick or electrical switch, that enables independence); "require adaptive seating for pelvic and trunk control" [6]
Level **V**	Transported in a manual wheelchair	Non-ambulate, totally dependent in all aspects of daily living, activities and participation

Postural correction of the knee flexed contraction/ stiffness and deformity was achieved by the following surgical interventions: hamstring lengthening (hamstring/ pes anserinus lengthening and femoral biceps tendon transpositions) in 12 cases, combined with posterior knee capsulotomy in 8 cases, followed by traction and/ or casting, respectively resection of the neurogenic heterotopic ossification.

In the case of irreducible knee stiffness (flexum above 100^{0}) or in those in which physical therapy hasn't been able to obtain less than 80^{0} of the extension deficit, a 2nd step surgical approach was performed: the first surgical intervention, consisted of tendons transposition, was followed by 3 months of physical therapy, leading up to a 30^{0}-40^{0} of extension deficit, then a second orthopedic intervention, consisting of posterior capsular disinsertion (fig.1 and 2).

Results Pre-/ and postoperative outcomes and global functional status of patients with chronic knee flexion contracture are presented in Table II.

Table II. Pre-/ and post-surgical global functional status (on the adapted GMFCS-E&R scale)

GMFCS (– E&R)	Level I	**Level II**	**Level III**	*Level **IV***	*Level **V***
***Pre**operative*	0	0	0	77%	23%
Postoperative	0	**50%**	**50%**	0	0

Pre-surgical assessment: all patients had severe knee flexion contracture and stiffness. About 77% subjects were severely limited in their walking ability, being assisted in wheelchair (adapted GMFCS-E&R: level IV), respectively 23% were non-ambulate, being totally dependent in all aspects of care (adapted GMFCS-E&R: level V).

After knee orthopedic serial interventions, coupled with iterative, subsequent, individualized neurorehabilitation treatment, all subjects regained an almost complete knee extension (corrected to less than a critical 15^{0} angle of flexion). Half of them were able to ambulate using a knee-ankle-foot orthosis, with or without crutch(es) or waking frame (adapted GMFCS-E&R: level III) support. The other half regained the capacity to walk independently without help, on flat surfaces (level II).

For a better illustration, we present patient DF (meta-initials), male 27 years-old. Medical history and neurological evolution: he submitted a severe TBI (in Oct. 2014), followed by vegetative state (in Feb. 2015), and minimally conscious state (in Aug. 2015).

He was admitted in the Neurorehabilitation Clinic in different evolutionary moments after iterative, corrective surgical interventions for bilateral knee flexion contractures (fig.1, 2, and table III), presenting gradual improvement of his neurological status and on the adapted GMFCS-E&R scale.

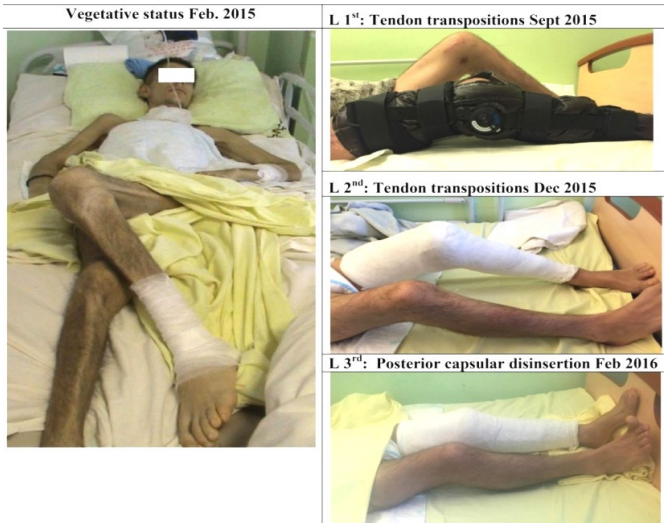

Fig.1. Patient DF (meta-initials), male 27 years-old. Flexion contraction in both knees (more severe in the left lower limb). Postsurgical evolution of the left knee after successive orthopedic corrective interventions (**L1st,L2nd,L3rd**), presented in Table III. Postoperative improvements in the right knee: noncritical flexion contracture, fewer than 15^0, subsequently addressed with kinetotherapy and knee orthosis.

Table III. Schematic synopsis of iterative orthopedic interventions (patient DF (meta-initials), fig.1 and 2

Right Knee	Left Knee
	16/09/2015 hamstring release (tendon transposition)
07/10/2015 hamstring release, orthotic device	
04/11/2015 excision of heterotypic calcification around the knee + medial collateral ligament transposition	
	07/12/2015 tendon transposition + excision of heterotypic calcification
	14/02/2016 posterior capsulotomy, ossification excision, manipulation under anesthesia (followed by casting)

Fig.2. Patient DF (meta-initials), male 27 years-old (Oct 2015). Good recovery after the first couple of bilateral successive orthopedic interventions: partial correction of knees flexion contractures. Postoperative rehabilitation outcomes: **Level III** on the adapted GMFCS-E&R scale, possibility to exercise (indoor) walking in household perimeter for limited distances, with long mobile orthotic devices and human assistance.

Discussion The hip and knee joints have essential biomechanical role for gait, by flexing and rotating, providing stability during the activities of daily life. Human normal posture and motility devolve upon extensive cinematic mechanisms and subtle sensorial tuning loops for balance recovery and control (**fig.3**).

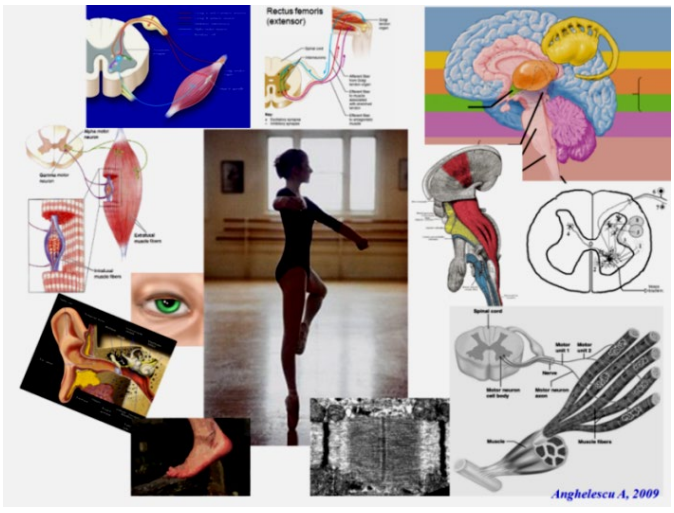

Fig.3. Functional interrelation, subtle sensorial tuning loops, cinematic mechanisms of balance and motility and interdependence in the Neuro-Myo-Artro-Kinetic (NMAK) apparatus.

These implied inseparable functional interdependence of at least two main systems (the

nervous and muscular ones) integrated in neuro-muscle-skeletal complex interrelations. The synergic collaboration of the afore mentioned systems is reflected by the modern concept of "Neuro-Myo-Artro-Kinetic (NMAK) apparatus, who`s functional unit (named the "kinetic unit") is composed at segmental level by the morph-functional triad: nerve – muscle – joint. Disruptions at any level of the NMAK apparatus may induce extensive dysfunctional biomechanical alterations (1-3, 9).

Spasticity is a disabling problem for many adults and children with a variety of neurological disorders such as multiple sclerosis, stroke, cerebral palsy, traumatic brain or spinal cord injuries. When the appropriate stretching is not carried out systematically in these patients, muscle shortening and contractures can occur. Spasticity causes pain, contractures, and impaired function. Ultimately, patients experience loss of function and mobility, hygiene difficulties, and orthopedic deformation (1-3, 9-17).

Severe central nervous system (CNS) lesions, usually (mainly) affect descending pathways, including the cortico-spinal tract. Lesions of the upper motor neuron cause imbalance between the excitatory vs. inhibitory stimuli, which converge to the peripheral neuronal pool (alfa and gamma lower motor neurons) in the spinal cord. Besides paralysis with specific topography, the affected muscles will become immobilized in a shortened position (10), and postural imbalances between agonists / antagonists / synergists / stabilizers occurs. In immobilized muscle occurs an increase quantity of connective tissue that reduces muscle compliance (11) and alters the rheological properties of the muscle, its plasticity and viscous-elasticity.

Disturbed rheological intrinsic properties of the muscle and the pathological disruption of the regulatory mechanisms interact with the limb control, position and movement. Resistance in recent-onset spasticity is reflex-induced, whilst resistance in chronically spastic muscle involves rheological changes, contracture, fibrosis, stiffness and atrophy (6, 9-22). Spasticity aggravates contracture and vice-versa, in a vicious cycle, resulting dysposturing, secondary severe myo-tendo-ligamental and joint-capsulo retractions, joint complications and limb dysfunctional problems. These disturbances usually represent targets/ therapeutic objectives for (Neuro-)Rehabilitation, are addressed in multi-/ interdisciplinary corrective interventions, and therefore represent the subject of this communication.

Pending on the two main path-physiological clinical models of spasticity – the spinal (tetra-/ paraplegia) or cerebral model (hemiplegia) – presence of co-morbidities, acquired complications, economic and technical endowment, different therapeutic procedures are indicated.

Sometimes neurosurgical interventions may be indicated, when spasms and spasticity cannot be satisfactorily controlled by medication and physical therapy (11, 19): neurotomy, rhizotomy, myelotomy, cordectomy, spinal cord stimulation, intrathecal baclofen or/ and morphine pumps.

The indications for orthopedic surgery are:

1.deterioration or uncontrollable spastic posture;

2.fixed deformity that interferes with function

3.secondary complications such as bony deformities, dislocation of the hip and/or joint instability (19).

Severe flexion contractures involving the knee or the hip represent major impediment to functional weight-bearing and ambulation, and the management of such deformities is challenging and problematic (4, 18-22). Significant knee contractures ($\geq 30^0$) are difficult to brace and severely limit standing and functional efficient ambulation.

Chronic (fixed) knee flexion contracture, elbows and/or hip ankylosis, or periarticular heterotopic ossification represent major challenges in the therapeutic management of patients with sequelae after CNS catastrophic traumatic events. Posterior capsulotomy addressed to a distorted, flexed knee joint, corrects the limb axis and expands the ROM (by the angle of the eliminated flexion contracture), and even may restore the patient's ability to walk. This orthopedic technique, followed by sustained postoperative rehabilitation, has a decisive influence on obtaining good functional results (4, 19, 22, 23).

Provided the deformity is controlled by other measures, there is no urgency about operations. In some cases, it may be better to delay until patients stabilise and then correct them in 1–2 steps (19).

Comprehensive preoperative assessment and goal setting in patient-centred multidisciplinary team, carefully evaluation of the general status, prophylactic and curative management are essential objectives of the physical and occupational therapy, oriented to secondary and tertiary prevention and

limitation of the complications. Respecting careful selection criteria, almost all of our subjects succeeded to provide good outcomes (Table II).

Braces and serial casting were used to maintain a spastic limb in a reflex-inhibiting posture and prevent relapsing contractures.

One of the main conditions for a possible orthopedic corrective intervention is represented by a stabile biological, clinic and functional somatic condition. Most of our cases have resulted from polytrauma events, and were admitted to neurorehabilitation with "poor" or "depleted" biological reserves, malnutrition or even "complex cashexia"(24), so these are patients at risk. In this context of frail biological general status, orthopedic interventions are not risk-free (especially procedures necessitating extended articular approaches).

In afore presented small group of patients, no post-acute orthopedic complications occurred. Any pathological situation (thrombophlebitis, respiratory or digestive infections, including sepsis with multiresistant drugs germs, or pressure sores) represent contraindications – at least temporary – for orthopedic surgery

Even in cases where conservative therapy is apparently overcome, general and focal myorelaxant treatment for the spastic somatic muscles might be effective. The case reported below is illustrative (fig. 4, 5).

Fig.4. Patient BRC (meta-initials), male 23 years-old (Apr 2018). Medical history and neurological evolution: in Oct 2007 he submitted a severe TBI (diffuse axonal injury – DAI) after hetero-aggression. He was hospitalized for 6 months in Spain and then transferred in our clinic in Apr. 2008, in a chronic stage, with severe neuropsychological impairments: spastic tetraparesis (right hemiplegia), posttraumatic encephalopathy, mixed non-fluent aphasia, neurogenic bladder.

Important somatic impairments: flexion contractures involving the knees, hips and elbows. Apparently irreducible contractures: right knee fixed contracture (125º, mAS 4), flexion of the 4th and 5th fingers of the right hand („pseudo-cubital paresis"), and irreducible varus equin of the left foot.

Cerebral MRI: diffuse cortical atrophy, bilateral hippocampus atrophy, lacunae in the mesencephalon. EMG: normal bioelectric parameters of the right cubital nerve, excluded a peripheral lesion.

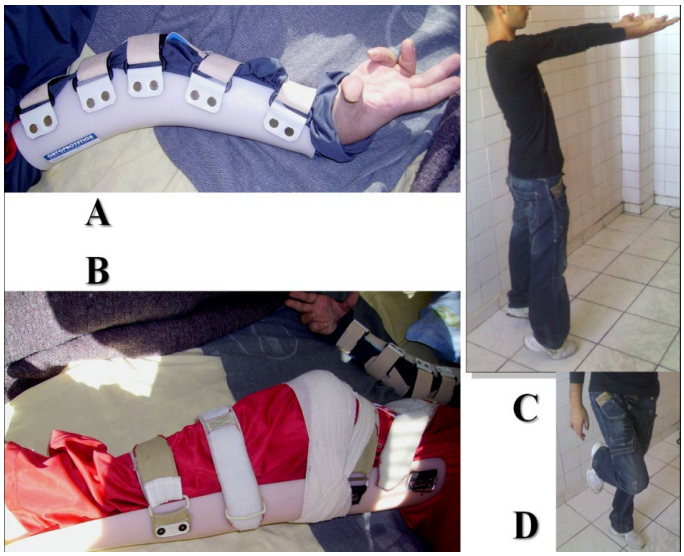

Fig.5. (A,B) Patient BRC (meta-initials), male 23 years-old (Dec. 2008). Systemic miorelaxant treatment (dantrolene 50 mg/day) and focal chemodenervation with botulinum toxin therapy 1500 UM Dysport, addressed to the right upper limb and both lower limbs), followed by sustained kinetotherapy and deposturing ortosis (maintained for 6-8 hours daily).

At discharge (after 8 weeks): unipodal walking with the roller frame. At 16 weeks: bipodal walking, using the roller frame.

Fig.5 (C,D). Patient BRC, male 24 years-old (Apl 2009), after 12 months. Independent for basic ADL, substantial neuropsychological improvement. No motor deficit, good orthostatic posture, able to maintain monopodal balance (D), and rise on tip toes (C). Total dissipation of the contracture in his right hand.

Essential medical information and educational endeavors linked to the individual pathology are provided for both the patient and caregivers, who are taught to avoid pathological postures, and prevent complications.

Sometimes (especially in patients with vegetative status), the last / unique therapeutic solution for these joint contractures remained the palliative orthopedic approach, for severe dysposturing

contractures that interfere with shoe wearing, wheelchair positioning and/or personal hygiene.

Conclusions Chronic (fixed) knee flexion contracture, elbows and/or hip ankylosis, or periarticular heterotopic ossification represent major therapeutic challenges in the management of patients with sequelae after CNS severe traumatic events.
Comprehensive, inter-/ multidisciplinary collaboration between the orthopedic and neurorehabilitation doctors and connected multi-profesional teams are essential for complex therapeutic approach of patients with severe limb contractures. Orthopedic intervention is only a part of the ensemble of the necessary corrective therapeutic procedures.
Proper evaluation and goal setting are mandatory for the rehabilitative management, pre-/ and post orthopedic corrective surgery. Harmonized timing for iterative interventions, followed by postoperative structured and sustained (often for life-time) rehabilitation programs are essential for obtaining best possible functional results. Adequate prophylaxis of complications represent a main therapeutic objective.

Abbreviations:
mAS, modified Ashworth scale
CNS, central nervous system
DAI, diffuse axonal injury
GMFCS (–E&R), Gross Motor Function Classification System (Expanded and Revised)
NMAK, Neuro-Myo-Artro-Kinetic
ROM, range of motion
SCI, spinal cord injury
TBI, traumatic brain injury

All authors have made substantial contribution to the work, and approved it for publication.

Conflicts of interest
The authors do not have conflicts of interest to declare.

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The importance of visuo-motor coordination in upper limb rehabilitation after ischemic stroke by robotic therapy

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Abstract

Stroke is an acute hypoperfusion of cerebral parenchyma that most often leads to outstanding motor deficits that can last for the rest of the patient's life. The purpose of the neurorehabilitation process is to limit, as far is possible for the motor deficits and to bring the patient to an independent life. A modern method consists in robotic neurorehabilitation which is more and more used, associated with functional electrical stimulation (FES). At the lower limb, the use of robotic rehabilitation associated with FES is already considered a success due to relatively stereotypical movements of the lower limb. In opposition, the upper limb is more difficult to rehabilitate due to its more complex movements. Therefore, eye-hand coordination (EHC) constitutes an important factor that is conditioning the rehabilitation progress. The eye-hand coordination can be brutally disturbed by stroke with critical consequences on motor-executive component. The EHC development depends on the interaction between a feedback complex and the prediction of the upper limb motility in the space, and requires the association between visual system, oculomotor system and hand motor system. We analyzed the stroke impact on this sensorial-motor functional integration and looked for a possible solution for the interruption of coordination between eyes and the movements of the superior limb. We consider that our study can contribute to a better understanding and to a faster rehabilitation of the motor deficit in the upper limb after stroke.

Key words: *stroke, rehabilitation, eye-hand coordination, robotic neurorehabilitation*,

Introduction

Stroke is defined as a rapid onset of neurological focal deficit, symptoms caused by a vascular lesion of the cerebral parenchyma. The syndromes resulting are various and greatly depending on aetiology, severity, prognosis and recovery possibilities. Over the past 20 years an important changes in the early diagnosis, treatment and rehabilitation techniques were made (1-4). Stroke is the fourth killer and the first cause of adult long term disability in United States (US) (5). The worldwide impact of stroke seems to be more higher than it is in US (6). The rehabilitation interval has a window when the neuroplasticity is maximum, during which, the brain ability for rehabilitation is enhanced (5). In this context, robotic rehabilitation (RR), one of the most modern technique is intensively studied in this century along with using mechanotronics technologies and computer software development (7, 8). RR can facilitate and increase the efficiency of motor deficiency recovery therapies. It is currently one of essential therapeutic tools for restorative therapy of lost functions and return to functional independence in order to improve day by day activity for stroke survivors who experience limitation of mobility and communication (9). The results of a systematic review of studies that investigated the outcome after rehabilitation assisted by robotic therapy after stroke, compared with classical physical therapy was presented by Kwakkel et al (10). This study reveals a moderate but statistically significant better upper limb motor rehabilitation results for patients where robotic assisted therapy was used, compared with conventional therapy. In addition, computer assisted devices for regaining upper limb function can optimize the required movement pattern (10). By this technology, more personalized therapy, specific for

each patient needs, can be assigned better by robotics than by conventional rehabilitation methods. There are still more studies needed in order to differentiate the mechanism of rehabilitation in robotic assisted therapy, where is a recovery based on neuronal repair, and where is a recovery based on compensation strategies (11).

The functional outcome in stroke rehabilitation strategies has two targets: one dedicated to upper limb motor recovery, and one dedicated to lower limb motor recovery. Differentiation in applied rehabilitation strategies must take into account the spatial complexity of the upper limb movement, compared to the relatively stereotypic lower limb movement into environment. For the upper limb, movements are automatic or voluntary, goal oriented. For the lower limb there are rhythmic movements for the locomotion and gait (12). These differences are reflected in speed, amplitude and directions of movements for each part of the body, in a particular pattern, that can be controlled by robotic assisted therapy (12).

From a functional point of view, the robotic technique can be dedicated to mobilizing a limb with no function (type I) or mobilizing a limb with a partially lost function and still possessing a variable grade of muscle strength (13). Adding feed-back mechanisms can have a complementary role in improving rehabilitation, especially in prosthetic upper limb rehabilitation, due to empowering the users to correct their movements in order to get better results (14). Most of the clinical studies refer to the grasping force as a variable that can be controlled by feed-back when the patient vision is not able to evaluate it (15). Recent studies reported that it is possible to improve the efficiency of the feedback mechanism by introducing a somatosensory feedback and transferring the stimulus (without translation) directly to the peripheral nerve endings which are directly stimulated by this functional loop (16). An important conclusion regarding the sensiomotor assisted prosthesis with feedback function consists in ability of the patient to grade them the force of contraction, in order to execute a movement to a target, after the device is removed and after a proper training and a consistent quantitative acquisition of muscular force was made (17). The force generated after the device is removed is about 30-50% from the force generated with prosthesis (17). This aspect is important for self-training, because patient's satisfaction can increase the efficiency of rehabilitation therapy.

The aim of this paper is focused on analyzing the robotic rehabilitation therapy (type II technology), dedicated to upper limb rehabilitation, in order to improve its motor performances. The vault key of RR that offer flexibility to "human-robotic arm" interface is represented by biomimetics. We intend to create a basic framework and offer a new perspective, more advanced on human –technology integration, hopefully for improving therapeutic efficiency in stroke rehabilitation strategies.

Human-robotic interface – role in stroke rehabilitation

Engineering systems became more and more sophisticated and "intelligent". For a good functioning and respect for biomimetic principle, a robotic system must present three components: stimulating component, the possibility of recording the action potential and integration of the information (18). The training has to be gradual in amplitude and force in order to protect the joints (18). The Fugl-Meyer (FM) score at time of admission can be important for timing the rehabilitation procedures, shorter robotic training periods being helpful for patients with lower admission (FM) scores and greater upper extremity impairment, followed by longer training periods that can bring new improvements. Some of the patients can also improve their rehabilitation performances after the ending the robotic training (18).

Rehabilitation efficiency can be controlled by imagistic methods that can assess the progression of recovery of lost functions. Integration of robotic technology with brain imaging, especially those that are able to visualize the function of the brain could bring a real contribution to understand the rehabilitation process. One of the most used imaging technique is represented by positron emission tomography (PET) of the brain, that is able to visualise brain activity in different tasks that imply different brain areas functioning. For an adult subject (right handed) there are early learning process and late learning process each of these processes involving different cortical areas (13). Due to continued advancement of radioligands and due to recent integration of PET and magnetic resonance

imaging (MRI) a new window for exploration of brain function was opened. MRI having a better spatial and temporal resolution can substantial contribute to functional assessment of the brain during rehabilitation process, through functional MRI exploration variant (19). Both of techniques are able to capture a designed activity of the brain during learning process of manipulating objects by robotic devices and to observe the brain areas involved in these specific activities. There are reports which describes that PET assessment can be helpful for giving metabolic and blood flow information regarding the learning process due to rehabilitation, revealing that the cortico-striatal loop is important in early learning while the motor execution areas played a significant role during late motor learning (cortico-cerebellar loop) (20). As patients became more skilled at the motor tasks, the functional neural networks activity is commuted to the cortico-cerebellar loops, with a significant increased activity in left premotor, left primary motor, and sensory areas, and in the right cerebellar cortex. The same study conclude that patients with basal ganglia lesions would take longer to start the recovery process due to deficiency of early phase of learning process, and patients with lesions in motor-execution areas will slowly recover due to deficiency in the later phases of learning process (21). The smaller is the number and size of the lesions of those areas following stroke, the better outcome is expected (20). All of these data should be taken in consideration and they can't constitute a general rehabilitation pattern due to various co-morbidities associated with each patient that can limit the patient recovery (22).

The stimulating component of robotic rehabilitation technique must assure that the device is applying an adequate electrical stimulation at one motor point of muscle. This has to be assign in order to recreate a spatial model of neural activity in which the specialist wants to replace or improve. Lo Ac et all designed a protocol for active therapy with controlling the duration, the intensity, the methods, and the time applied of rehabilitation program, in order to improve the reproducibility of training for stroke survivors (taking into the study, moderate to severe affected patients) (23). But electrical stimulation presents a major inconvenience, related to multidirectional spread of electrical current into a tissue, resulting a global stimulation and loss of structure selectivity which must be stimulated (23). This inconvenience can be diminished by choosing a proper stimulation parameters, by using of an appropriate electrodes and by the the correct choice of stimulation (10, 23).

The recording of action potentials, for the robotic arm device, is also an important component of robotic rehabilitation process. The coordinated movement involves a two ways shifts (nervous command from the central nervous system to the muscles and a feed-back from the muscles to the central nervous system). This circuit allows continuously adjusting the muscles contractions to the required parameters (24). In the case of using a robotic arm, the feedback currents are very weak and is lost in background electric noise. This is the reason why the robotic rehabilitation device requires special sensors to appreciate the degree of muscle contraction produced by functional electrical stimulation (FES), or to appreciate the amplitude and the speed of the movements performed by robotic arm (18). A possible problem would be the increasing of the weight of the robotic arm by monitoring of too many sensors.

The integration of information play an essential role in robotic rehabilitation methods. Due to complexity of motility of the human body, the fine control is achieved through the integration of a lot of information from environment into the central nervous system (the information are intermediate by mechanoreceptors from muscles and joints, by visual system and vestibular system sensorial reception) (24). A self-organized and self-adaptive system of great complexity is achieved where the motor scheme is gradually composed due to the training process, a scheme by which the central nervous system is trying to compensate the motor disability thorough a force imposed by the environment (25). In order to be able to control the movements this system respects the following rules: finite state control, proportional control, compensated control, predictive control (24, 25). The models that incorporate and use these principles of feedback control, actually are represented in neurological terms by the plasticity of the central nervous system. Such a complex system gains the flexibility in performing motor task even after destructive lesion as are after stroke lesions, this process being named use-depend neuroplasticity, and is considered a basic goal in neuro- rehabilitation therapy (26). Mawase et al found that the action repetition while learning a motor task enhances use-dependent neuroplasticity (26).

The developing technique of the functional electrical stimulation is recorded in numerous studies. The development effort in this research field started 29 years ago and aimed to restore the motility in paraplegic patients (27). Rehabilitation of motor deficit in the upper limb represents a much greater challenge, considering the degree of kinetic complexity (28), but decoding the algorithms for the functioning of the neuromuscular unit remains an open challenge. In our opinion, the greatest problem of the using of functional electrical stimulation coupled with robotic arm is the lack of coherent and continuous feedback between amplitude of performed motion, and the algorithm of electrical stimulation applied to achieve optimal coordination during the movement of distal extremity of the robotic arm. We suggest there are three possible solutions. The first suggestion is the placement of contraction sensors or angular displacement sensors on the healthy contralateral upper limb. In this hypothesis, the coordination of the dysfunctional upper limb assisted by functional electrical stimulation is obtained by imitation movements performed by the healthy upper limb (which actually occurs within imitation synchinesis). This process is possible due to and mirror neurons functions first identified in the ventral premotor cortex (PMv; area F5) and later in the inferior parietal lobule (areas PF and PFG) of monkey brain, namely "mirror neuron" system and having an important role in motor rehabilitation and aphasia recovery after stroke (29). The second suggestion is the placement of some sensors on robotic rehabilitation device that can respond to a present voice command. A single voice command can, thus, increase and decrease the level of electrical stimulation applied to a muscle or more muscle units and resulting in increasing or decreasing the device power. Both first and specially the second method could have a strong therapeutically effect. Meanwhile both of them can lead to achieving an intense cognitive mobilisation and voluntary conceptual forming of the entire rehabilitation process, in order to control the desired voluntary movements. In this way, patient's involvement into the rehabilitation program, for developing a voluntary movement is greater, due to volitional component which is enhanced. The last suggested solution is the placement on the head and eye a position sensors which follows the distal extremity of the robotic arm, and modifies the functional electrical stimulation parameters. The last solution seems to be most suitable to physiological condition of adaptive process to the environmental stimulation. This solution restores visual control of the complex motor function of the upper limb into the space. The robotic-arm-eye connection via functional electrical stimulation actually reinforce the lost functional connection between eye and hand which is essential for movement coordination (30). If eye-hand coordination recovers through sensors and functional electrical stimulation, there is possibility for a more rapid progress in neurorehabilitation.

A more clear characterisation of eye-hand coordination regarding the connection between ocular motor control and manual motor control will improve the understanding of its role in upper limb motor rehabilitation after stroke (31). Therefore eye-hand coordination (also known as eye-hand coupling, visuo-manual coordination or oculo-manual synergy) physiology is defined as the coordinated control of eye movements associated with the fine movements of the hands toward a given target, reaching the target and performing the desired work (32). Good directed movements of the upper limb is provided by a large number of neural mechanisms: detection of the target in a three dimensional space (by visual perception), space assessment of the body and of the upper limbs, evaluation of the muscle tone (by proprioception) and execution on-line guidance of the hand trajectory (33-35). In fact, the essence of eye-hand coordination is the result of the very detailed coupling in space and time of kinetic learning mechanisms. An equivalent form of eye-hand coordination is found in all forms of life, being linked to the evolution of the visual system and its connections into the brain in order to assign species surviving (36,37). Evolutionary processes offers to the optic chiasm a particular importance due to crossing and non-crossing optic fibres structure that determines which hemisphere receives proprioceptive information about the ipsilateral hand (37). Multimodal neuron response to tactile as well as visual targets, and extensive use of multimodal sensory information supports the hypothesis that accurate upper limb control influenced the evolution of the primate visual system and consequently evolution of the brain. This hypothesis is named eye-forelimb hypothesis and consists in evolutionary change toward hemidecussation in the optic chiasm, providing the

evolution of frontal vision and visually guided forelimbs (37, 38).

The afferent component of eye-hand coordination is important for the adequate function of this entity. The visual system is equipped with remarkable ability of detection and localization of the targeting objects (stationary or mobile). For mobile targets it is able to appreciate the speed, the trajectory, and can anticipate the position of the target in certain moment. There are currently an impressive numbers of researches that have as an objective the motor behaviour of the eyeballs when are pursuing an object and modern imagistic techniques for brain activity assessment, as is functional magnetic resonance imaging, can bring a new inside into this research field (39- 41). The line of sight follow the target and always keep it in the centre of visual field at the fovea level (35). At this level, the photoreceptors density ensure the best visual resolution for a 2-3 degree angle of the visual field. The foveation consists in centring of an object of interest onto fovea (35). This process is made by different mechanisms, depending to the distance to which the object is located. If the object is near the face, in the frontal plane, foveation is achieved by convergence phenomenon that is coordinated by the brain (42). But if the distance to the object is longer or if the object is moving fast, foveation is achieved by movements (possible rapid) of the head, in order to ensure the eye-hand coordination process or saccadic eye movements are onset (43). Both mechanisms contribute to the stabilisation of the line of sight on the target and to the target's projection on the fovea. Due to these mechanisms the eyes are able to pursue an object, and visual information is transmitted to the cortex, in order to guide the direction and the distance of movements for a specific action (35). The targeting time is variable. Sometimes the eyes remain fixed on the target until the motor action is finished, or, in other situations, the eyes are moving for pursuing another target, before the hand is reaching the object. Hand movement is performed in this case automatically in the absence of foveal control. This phenomenon is related to visual anticipation of the future kinetic plan and requiring the visual memory (44). In another circumstances, the line of sight returns to the original, due to the visual memory reinforcement (45). Sometimes, in the case of automatic movements with a well memorized kinetics, and when specific movements are frequently performed, the visual system offer a three dimensional support of the frame in which the movement is taking place. The kinetics of the hand can thus unfold at the periphery of visual field and fovealization is not necessary. By all of these mechanisms the human visual system is able to recognize different objects in different instances, and to transmit proper information to the brain in order to achieve an adequate decision regarding the future actions (46).

Eye-hand coordination abnormalities after stroke – importance for rehabilitation process

There are several abnormalities of eye-hand coordination that can occur in stroke survivor's patients. There can be a change in latency of saccades initialization for a target pursuing, comparing with control subjects (saccades occurs earlier). This can be due to upper-motor-neuron-like desinhibition phenomenon, in which, patients with cerebrovascular lesions anticipate the movement in spite of the instruction to the contrary (30).This phenomenon has as an explanation the inability to suppress saccades, that are maintained as a reflexively, in response to a target (initialization of saccades takes about 60 ms that are needed for the information to travel from the retina to brainstem where the command for extraocular muscle is made in order to initialize saccades ; the saccades are onset after 200 ms, the differences being attributed to the cognitive process to analyze these information and make a decision) (47). In stroke patients there is an anticipation of saccades which occur earlier than 60 ms (47). The motor control of the movements is more complex, because each movement imply visual contribution and saccades adjustment, in order to reach the targeting object, to touch it, to grip it, and eventually to lift it according with its size and weight. All of these action needs a modulation of saccades output (48). There are also different abnormalities regarding the eye-hand coordination, as are spatial errors leading to saccadic dysmetria associated with the lesions in cortex, pretectum, thalamus, superior colliculus, and cerebellum, where the patient can't predict the distance to the target or the size of the target (49, 50). There is also an alteration of predictive control which is essential for planning a visuomotor action. After stroke, the patients can experience the inability to program motor action sequences in space and time (51, 30).

Conclusions

The ocular motor system can constitute a sensitive marker, in ischemic stroke, for motor and cognitive recovery. The environmental perception with visual system has to be transposed in a precise motor action designed to a day by day living. Eye-hand coordination is an accurate circuit that serves to this goal. Understanding and improving eye-hand coordination can have an essential contribution role with clinical implication for a better and proper rehabilitation strategy post stroke. Despite the fact the brain lesions were considered mostly definitive, the neuroplasticity phenomenon proved that a proper training can recover partially lost or diminished functions. Future studies are needed for analyzing various techniques of rehabilitation, in order to organize a valuable scheme for the best outcome. There is a serious challenge to bring all the information in practice and offer to the patient a training model that can be comfortable and can bring real improvements for their disabilities. Informatics development and robotic techniques evolution, together with the possibility to make more and more brain functional mapping due to modern imagistic techniques, could bring for these patients, a new hope for improving their quality of life.

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Study on the importance of medical treatment and physical methods in recovering patients with knee osteoarthritis

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Abstract

Intrduction.Etoricoxibum belongs to the group of non-steroidal anti-inflammatory inhibitors selective of cyclooxygenase-2. The non-steroidal anti-inflammatory drugs are used to treat acute musculoskeletal disorders as they result in pain-relieving therapeutical effect. Etoricoxibum intervenes by blocking cyclooxygenase-2 and by reducing the painful and inflammatory phenomena. **Material and method**. The trial focused on the evolution of patients diagnosed with knee osteoarthritis after making the treatment by etoricoxibum. This study was conducted in the ambulatory regime for a period of 6 months and included 77 patients. **Results and discussions** It was assessed the efficacy of the complex recovery treatment for the patients diagnosed by knee osteoarthritis wich use of Etoricoxibum, in a dose of 60 mg /day, in order to improve the pain and the inflammation. The pursued objectives were: the assessment of the effects by using Etoricoxibum for the reduction of the pain and inflammation, the increase of the articular mobility and stability, the recovery of the walk and motor control, the decrease of the body weight, the increase of the quality of life. **Conclusions.** This trial show that, by making a combined treatment of medication and recovery, there was an reducing the pain and the inflammation as well as increasing the articular mobility.

Key words: *osteoarthritis, pain, ultrasound, recovery, disability*,

Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medicines that belong to the category of the non-opioid analgesics. They have a high safety profile, a low risk of side effects and medicine interactions.

The NSAIDs inhibit reversibly the cyclooxygenase (COX), an enzyme that is involved in the synthesis of prostaglandin, at the central level and at the peripheral one. This enzyme can be found in two types, namely: cyclooxygenase 1(COX-1-involvedin the physiological secretion of prostaglandin, being a platelet antiaggregant and having the role to protect the intestinal mucosa) and the cyclooxygenase 2 (COX-2- having a role in the secretion of the prostaglandins that are involved in the painful and inflammatory processes).

The inhibition of COX-2 leads to the anti-inflammatory, antalgic and antipyretic effect. The inhibitors of COX-2 are specific inhibitors, called coxibi (1), that have a low risk of digestive side effects towards other NSAIDs, but with a certain cardiovascular risk, that is why caution is imposed while giving it to certain patients.

The NSAIDs are greatly used in the treatment of the muscular-skeletal conditions. It is worth noting that over 80% of the population aged over 55 (2) presents radiologically modified joints. Such a modification is osteoarthritis, a progressive invalidating condition, having a degenerative and chronic character that affects the articular cartilage, the subchondral bone, the articular capsule, the hypertrophy of the marginal bone with the formation of osteophytes (3, 4).

The most frequent affected joint is the knee, involved in maintaining the static and dynamic balance, the walk and the orthostatic stability (5). The clinical and functional symptomatology includes pain, limitation of articular mobility, crepitating, deformation, instability, decreased of the functional capacity, affecting the walk and the posture(6, 7). Due to the functional deficit caused by the disease, the knee osteoarthritis is considered a health issue (8). In osteoarthritis are involved the cytokines -Interleukin 1 (it increases the protease release and it can inhibit the proteoglycan synthesis), Interleukin 17 (it stimulates the synthesis and enables the release of the pro-inflammatory cytokines), TNF-alpha that can deteriorate the cartilage. In order to have a good diagnose we have to take care of the quality of

biochemical parameters analysis and the correct interpretation of the results, respecting the reference limits (9).

According to the revised ACR criteria, the physical exercise is very important in the recovery, beside the use of NSAIDs. There are trials which show that, by making a combined treatment of medication and recovery (5), there was an attempt at reducing the pain and the inflammation as well as increasing the articular mobility.

A trial of 2011 (10) focused on the evolution of 39 patients with knee osteoarthritis who made physiotherapy and were evaluated according to WOMAC and Lequesne scales, to the "stand up and walk" test and the 6 minutes' walk test. Except for the WOMAC scale, all the other results were significant. The recovery treatment is supposed to have modern physiotherapy techniques that prevent, fight and recover the redness in the joints, the faulty precarious and tissular regeneration as well as the functional deficit (11). The electrical therapy techniques (low frequency currents - galvanic, diadynamic, Trabert, TENS, average frequency -interferential) are some of the most used methods of physiotherapy (12). Its purpose is to obtain antalgic and anti-inflammatory effects. It is very efficient when associated to other procedures (e.g. ultrasound) (12, 13).

The ultrasound treatment enables the transmission of the pendular mechanic vibrations, their penetration and absorption in the human body. The ultrasound has the qualities of being fibrinolytic and muscle relaxant (14, 15). The pathogenesis of osteoarthritis refers to the excessive loading of the joints and to the modification of the biomechanics models together with the deregulation of the hormones and of the cytokines (16, 17). The kinetic therapy has the purpose of preventing the muscular atrophy of the bilateral quadriceps, to tonify the musculature, to repair the dynamic control for a good static posture but also for the walk, to repair the articular mobility (18, 19). Moreover, at the psychical level, the physical activity, by the synthesis of neurotrophins and the improvement of neuroplasticity can have a beneficial contribution in the neurodegenerative diseases, respectively in the slight cognitive disorder (20). Cochrane showed in 2015 the importance of the physical activity in order to improve the pain and the functional condition for persons with knee osteoarthritis (21). Nevertheless, the small number of trials does not point out the minimal intensity of the physical exercise programs necessary to demonstrate the clinical effect.

Another trial (22) points out that the physical exercise is one of the non pharmacological methods recommended by international guidelines. The data were taken from 54 trials related to pain, physical function and quality of life. The proofs of the trials show that therapeutic exercise can be beneficial for a short term of 2-6 months, in comparison to the treatment by NSAIDs. Yet, in the chronic therapy made systematically, there have been numerous adverse reactions at the gastrointestinal, cardiovascular, pulmonary and renal levels (23, 24). It is preferred to use NSAIDs in the topic form instead of the oral administration but, in case of using topic NSAIDS, the level of the active substance in the blood is very low in comparison to the one of the oral administration (25, 26).

According to the recommendations of ACR/RACGP, the administration of non-selective NSAIDs or specific COX-2 is indicated in the moderate or severe osteoarthritis, in efficient minimal doses, taking into account that osteoarthritis has an undulating slowly progressive evolution, with acutisation periods.

According to the recommendations of ACR/RACGP, the optimal management of osteoarthritis is made by associating the non-pharmacological treatment to the pharmacological one. We tried this association in our trial, too (27).

The indications by Cochrane are for the administration of specific NSAID (Etoricoxibum) for patients who are at gastrointestinal risk (20). It is considered that Etoricoxibum has a more reduced power than the other NSAIDS, but it is preferred as it has fewer side effects (28). Etoricoxibum (5-chloro-6'-methyl3- [4- (methylsulfonyl) phenyl] -2.3'-bipyridine) belongs to the group of non-steroidal anti-inflammatory inhibitors selective of cyclooxygenase-2 (COX-2). Etoricoxibum intervenes by blocking COX-2 and by reducing the painful and inflammatory phenomena (29).

Objective

The trial focused on the evolution of patients diagnosed with knee osteoarthritis after making the treatment by etoricoxibum beside the complex recovery one.

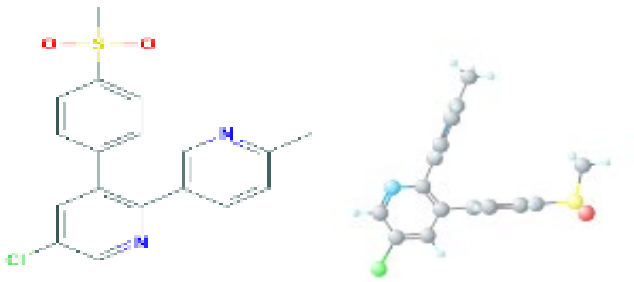

Fig. 1. The chemical formula for Etoricoxibum. C18H15ClN2O2S (PubChempubchem.ncbi.nlm.nih.gov)

Material and methods

The trial was conducted in the ambulatory regime for a period of 6 months and included 77 patients. They were informed about the trial and gave their consent. The trial complied with the valid ethics norms and with the deontological ones.

The exclusion criteria were: the chronic rheumatologic diseases (ankylosing spondylitis, rheumatoid arthritis, gut), the traumatic issues of the knee (fracture, luxation, sprain), younger than 45, neurological disorders present at the level of the lower limbs, decompensate cardiovascular and pulmonary disorders, persons who did not agree to participate in the trial. The inclusion criteria were: older than 45, diagnosis of bilateral knee osteoarthritis, minimum one-year-old disease, compliance with the treatment, return for the medical check-up, persons who did not receive physical treatment in the past 5 months, patients who gave their consent to participate in the trial. It was important to calculate the body weight index with the formula mass (kg)/ height $(cm)^2$. The treatment was complex: hygiene-diet (diet, movement and posture), pharmacological (administration of NSAIDs) and recovery. The patients received indications on how to follow the daily calorie regime according to their age, how to do activities aimed at keeping / reducing the body weight, the daily walking program (walk, going up/down the stairs), the correct posture from a static and dynamic point of view, to avoid standing up for too long, too many household/ professional activities as well as the wrong postures. From a pharmacological point of view, according to the same recommendations (to administrate NSAIDs in an efficient dose), the patients received treatment by Etoricoxibum in a daily dose of 60 mg.The used electrical therapy procedures were: the Trabert current (the fixed frequency of 140 Hz, the length of the impulse 2ms and the pause of 5ms), the current frequency average (the frequency de 80-100 Hz) for the anti-inflammatory/antalgic purpose. The applied ultrasounds had the frequency of 1 MHz and a power of $0.3W/cm^2$, a pulsatile form, by using an acoustic gel, without the active pharmacological substance, by applying it with circular movements, by using the applicator with the diameter of 5 cm. The recovery program included isometric exercises (with a ball and an elastic band), insisting especially on quadriceps and adductors. The assessment was made at the beginning and at the end of the treatment, but also at the control of 3 months. It consisted of a clinical examination, radiological investigations and knee ultrasound. Clinically the following were considered: the bilateral knee issue, the presence of the spontaneous pain the articular mobility, the inflammatory modifications at the level of the knee joint, the stability of the knee – static and dynamic, the alignment of the lower limbs, nutrition status, and muscular status.

Radiologically (*Kellegren Lawrance scale*) and by ultrasound the following were pointed out: a narrower articular space, frequently medial, marginal and posterior osteophytose, the subchondral sclerosis, deviations of the biomechanical axis of the sick lower limb.

The pain was assessed according to the VAS scale, the functional index and the articular redness were assessed according to the WOMAC scale whereas the articular mobility was assessed by means of the goniometer.

Before the beginning of the trial, the participants were informed and gave their participation consent.

The pursued objectives were: the assessment of the effects by using Etoricoxibum for the reduction of the pain and inflammation, the increase of the articular mobility and stability, the recovery of the walk and motor control, the decrease of the body weight, the increase of the quality of life.

The statistical analysis

The data were recorded in folders in Microsoft Excel; the average, the median, the standard deviation and the t-student test in order to compare the obtained results and in order to see whether the work hypothesis was confirmed. Thus, after calculating the t-student test, there was considered the value of the p index that shows the possibility of an occurring error related to the hypothesis.

Results and discussions

The participants to the trial were divided into 2 groups, namely: group1 who received low frequency currents (the Trabert current), frequency average (interferential), ultrasound and kinetic therapy (n= 40) and group 2 (n=37) who also received (in comparison to group 1) treatment by NSAIDs selectively, respectively Etoricoxibum of 60 mg/day for 14 days. For these groups, the characteristics are found in Table 1.

	GROUP 1		GROUP 2	
AGE	58.5±8.45		59±8.78	
AGE GROUP	women	men	women	men
(45-54) years	8	3	3	4
(55-64) years	11	6	9	6
(65-74) years	7	2	6	5
>75 years	2	1	2	2
TOTAL	28	12	20	17
patients	40		37	
BODY WEIGHT INDEX	28.88±3.05		28.24±2.99	

Table 1. A presentation of the trial groups

It is found in both trial groups that the most affected age group was 55-64 years, whereas the female patients were the most affected ones (28 in group 1 and 20 in group 2), in comparison to the male patients (12 in group1 and 17 in group 2). The pain assessment led to the analysis of the obtained results after using the VAS scale, but also the pain assessment segment in the WOMAC scale.

The visual analogue scale for the pain assessment (VAS) cuantifies pain from 0 (the absence of pain) to 10 (the maximal score for pain). By using this scale the patient can observe pain in the assessment moments (Table 2).

VAS	GROUP 1			GROUP 2		
Moment	Initial/Final	Final/Control	Initial/Control	Initial/Final	Final/Control	Initial/Control
T-student test	0.0111	0.0027	0.0009	0.0143	0.0276	0.0065

Table 2. The value of the p index calculated for the analysed moments (VAS scale)

For group 1 the pain was reduced by 21.5% at the end of the treatment, by 9.82% between the end of the treatment and control, and by 28.58% between the beginning of the treatment and control after 3 months. In group 2 the pain was reduced by 25% at the end of the treatment, by 33.4% between the end of the treatment and control, and by 50% 3 months after the beginning of the treatment. Thus it was found a reduction of the pain assessed by means of VAS scale, for both trial groups, significant in group 2, especially at the control moment versus final moment, $p<0.05$ (Table 3) (Fig.2, Fig .3).

		GROUP 1			GROUP 2		
SCALE	Moment	Initial	Final	Control	Initial	Final	Control
VAS	Median/dev.std	7±1.23	5.5±1.31	5±1.56	8±1.31	6±1.01	4±0.79
WOMAC	Median/dev.std	14.5±3.61	111±2.68	7±0.49	15±2.06	10±2.39	8±0.53

Table 3. The evolution of the pain assessed by VAS and WOMAC scales

The WOMAC scale is used especially for the assessment of the impact that the disease has upon the patients in relation to 3 important elements: pain, articular redness and daily activities. The pain quantification is made from 0 (lack of pain) to 4 (the maximal value for pain), being assessed while standing up, sitting down or on the back, during the sleep, while going upstairs and walking.

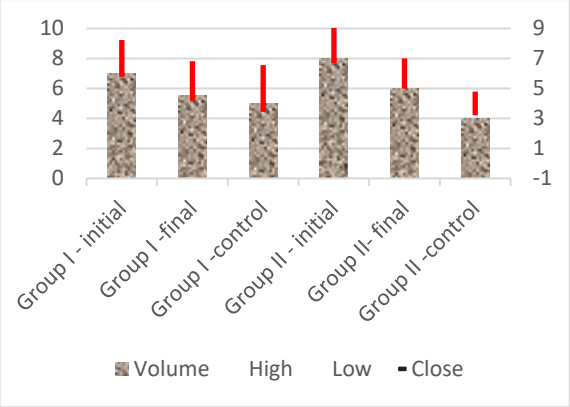

Fig. 2. The evolution of the pain for the two groups assessed by VAS scale

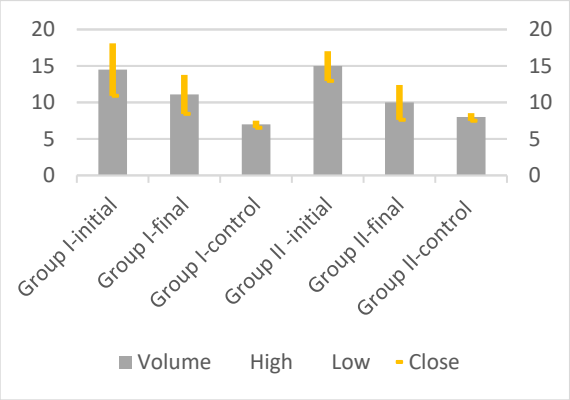

Fig. 3. The evolution of the pain for the two groups assessed by WOMAC scale

WOMAC pain	GROUP 1			GROUP 2		
Moment	Initial/ Final	Final/ Control	Initial/ Control	Initial/ Final	Final/ Control	Initial/ Control
t-student test	0.0168	0.0414	0.0109	0.0273	0.0157	0.0062

Table 4. The value of the p index calculated for the analysed moments (WOMAC pain)

The pain assessed by the WOMAC scale was reduced at the final moment of the treatment by 24.14% in group 1 and 33.34% in group 2. Between the final moment of the treatment and the control of 3 months, the pain was reduced by 36.36% in group 1 in comparison to 20% in group 2. Between the initial moment of the treatment and the control of 3 months,the pain was reduced by 52.73% in group 1 in comparison to 46.67% in group 2.

As for the value recorded on the WOMAC scale - pain, it is found that the value of this parameter was reduced in the two trial groups, whereas the values were more significant in group 2, especially at the control of 3 months after the beginning of the treatment, the values for $p<0.05$. The pain and the inflammation were reduced, as well as the prostaglandine, due to the administration of etoricoxibum in thedaily dose of 60 mg.

According to the WOMAC scale, the articular redness was assessed in the morning while waking up and during the day, while sitting down or lying on the back. The minimal value was 0 whereas the maximal one was 8.

In our trial the WOMAC scale showed a statistical evolution for the two groups and at all the moments, except for group 1 at the final moment when the obtained result is not significant. This can be explained by the fact that the patients of group 2 received NSAIDs with an antalgic and anti-inflammatory effect, by contributing to the reduction of the pain and inflammation, thus of the articular redness (Table5).

WOMAC redness	GROUP 1			GROUP 2		
Moment	Initial/ Final	Final/ Control	Initial/ Control	Initial/ Final	Final/ Control	Initial/ Control
T-student test	0.0232	0.0629	0.0156	0.0438	0.0138	0.0148

Table 5. The value of the p index calculated for the analysed moments (WOMAC redness)

The assessment of the articular redness recorded a diminution at the end of the treatment by 38.58% in group 1 in comparison to 42.86% in group 2, by 40% in group 1 and 25% in group 2 at the control of 3 months, and in an equal percent of 57.15% in the 2 groups at the assessment between the beginning of the treatment and the control made by patients after 3 months (Table 6).

WOMAC redness	GROUP 1			GROUP 2		
Moment	Initial	Final	Control	Initial	Final	Control
median/ standard dev.	7±1.15	5±1.64	3±0.48	7±0.91	4±0.59	3±0.51

Table 6.The evolution of the articular redness

Another discussed parameter is the daily activities quantified on the WOMAC scale. Some of the daily activities are: going upstairs/downstairs, getting on the car/getting out of it, walking on a flat road, doing easy/hard household activities, dressed/naked. The obtained results were significant at all the moments, especially at the control of 3 months, for both trial groups, whereas the value of p was lower than 0.05(Table7).

WOMAC- daily activities	GROUP 1			GROUP 2		
Moment	Initial/ Final	Final/ Control	Initial/ Control	Initial/ Final	Final/ Control	Initial/ Control
T-student test	0.0064	0.0176	0.0021	0.0092	0.0165	0.0027

Table 7. The value of the p index calculated for the analysed moments (WOMAC daily functionality)

As for the assessed daily activities done by the patients of the two groups, it was found that the articular mobility increased at the end of the treatment by 19.68% in group 1 in comparison to 22.81% in group 2. These values were relatively close during the control, of 30.62% in group 1 versus 29.55% in group 2, whereas the values at the initial assessment control were increased, of 44.27% in group 1 and 45.62% in group 2 (Table 8).

WOMAC- daily activities	GROUP 1			GROUP 2		
Moment	Initial	Final	Control	Initial	Final	Control
median/ standard dev.	61±2.25	49±3.08	34±1.69	57±3.23	44±3.26	31±1.26

Table 8. The evolution of the daily functionality

The articular balance at the knee level represented another parameter assessed during the trial. It was also found that all the results were significant with $p<0.05$, for all the trial groups and at all the moments, with more significant results at the control moment in comparison to the final moment of the treatment, which can be explained by the effects of using electrical therapy, kinetic therapy and NSAIDs (Table 9).

Groups		Flexion of the right knee			Flexiegenunchistang		
	Moment	Initial	Final	Control	Initial	Final	Control
Group 1	median/ std.dev.	79±17.76	87±17.25	93±18.07	80.5±17.0	90±15.58	98±16.15
Group 2	median/ std.dev.	86±12.35	96±13.46	110±14.96	80±15.97	93±14.72	110±15.26

Table 9. The evolution of the knee flexion

The increase of the knee mobility assessed by the articular balance recorded different increase for the two knees. As for the right knee, the values were higher in group 2 with 11.63% in comparison to 10.12% in group1 at the end of the treatment, of 14.58% in group 2 in comparison to 6% in group 1 at control, and significantly higher at the initial-control assessment of 27.91% in group 2 in comparison to 17.7% in group 1.

As for the left knee, group 2 has recorded valuesof 16.25% in comparison to 12.5% in group 1 at the end of the treatment, of 18.28% in group 2 in comparison to 9.45% in group 1 at the control, whereas at the initial-control assessment the values were 37.5% in group 2 and 22.36% in group 1.

This trial assessed the efficacy of the complex recovery treatment for the patients diagnosed by knee osteoarthritis and the use of Etoricoxibum, in a dose of 60 mg /day, in order to improve the pain and the inflammation. It is hereby easy to find modifications of the parameters assessed at the three assessment moments, especially at the control.

These results are similar to the ones in the specialty literature which show that it is possible to obtain significant benefits in the patients with knee osteoarthritis by using kinetic therapy, ultrasound or TENS (8, 30).

In the future, we are also looking for other modern therapy techniques. Raman spectroscopy will become a standard technique in osteoarthritis treatment. Raman spectroscopy is use for drop-coating deposition in osteoarthritis (31).

Conclusions

Osteoarthritis is the commonest form of articular disease and the main cause of the pain and of the physical disability in the elderly. The pain and the inflammation were reduced due to the administration of non-steroidal anti-inflammatory drugs but also due to the electrical therapy procedures (currents of low and average frequency, the use of ultrasound) with antalgic and anti-inflammatory character. The articular mobility as well as the static and dynamic stability improved due to the individualized program of kinetic therapy. An issue of the current trial would be the low number of patients but the results can be the starting point for future trials.

Abreviations

NSAID -The non-steroidal anti-inflammatory drugs

COX - cyclooxygenase

VAS scale - Visual Analog Scale for Pain

WOMAC scale - Western Ontario and McMaster Universities Osteoarthritis Index

RACGP - The Royal Australian College Of General Practitioners

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This study, being a retrospective one, did not require a written consent from the patients involved. All authors have read and approved this publication and had equal scientific contribution in publishing this material.

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The importance of early neurorehabilitation in the recovery of post-vaccination Guillain-Barre syndrome – a case report

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Abstract

Guillain-Barre syndrome (GBS) is the most common cause of acute flaccid paralysis worldwide, having an incidence of about 1/100,000 across several studies in a number of countries. We present the case of a 60-year-old female patient, with known hypertension, admitted to our department for paresthesia and muscle weakness predominantly in the distal upper and lower limbs. Symptomatology had an acute onset after 14 days from influenza vaccine administration. Lumbar puncture revealed CSF glucose (91 mg/dl), CSF protein (0.508 g/l) and no pleocytosis. Electromyography supported the presumptive diagnosis of polyradiculoneuritis. The patient underwent three sessions of double filtration and the final diagnosis was Guillain-Barre polyradiculoneuritis secondary to influenza vaccination. Approximately 80% of patients with polyradiculoneuritis recover completely within a few months to one year; however, 5-10% of these patients experience one or more recurrences. It should be emphasized that acute-phase rehabilitation must start immediately and include an individualized program of gentle strengthening, and manual resistive and progressive resistive exercises.

Key words: *polyradiculoneuropathy, influenza vaccine, neurorehabilitation*,

Introduction

Guillain-Barre syndrome (GBS) is the most common cause of acute flaccid paralysis worldwide, having an incidence of about 1/100,000 across several studies in a number of countries (1,2). GBS is thought to be an immune-mediated disease, in which antibodies in response to an antigenic stimulus, such as bacterial or viral infection, cross-react with nerve ending antigens (2). GBS became a major vaccine safety concern in 1976, when there was a threat of a swine-origin influenza pandemic and the United States government initiated a national vaccination program. After approximately 45 million people were vaccinated, an increased number of post-vaccination GBS cases were reported. The risk was found to be highest 2–3 weeks after vaccination. The attributable risk was estimated at 1 additional case of GBS for every 100,000 doses administered (3). In 2006, Juurlink et al. studied the association of GBS with influenza vaccines administered during 1992–2004 in Canada; using a self-controlled case series design, they found a small but significant increased risk of GBS in the 6 weeks following receipt of influenza vaccine (relative risk [RR] 1.45; 95% confidence interval [CI] 1.05–1.99) (4). In November 2009, prospective cohort analyses showed a small increased risk of GBS within 6 weeks of vaccination and an attributable risk of approximately 1 additional case of GBS per million persons vaccinated (5). Final analyses confirmed this small increased risk within 6 weeks of vaccination (6,7).

Case report

We present the case of a 60-year-old female patient, with known hypertension, admitted to our department for paresthesia and muscle weakness predominantly in the distal upper and lower limbs. Symptomatology had an acute onset after 14 days from influenza vaccine administration. At admission, the patient was hemodynamically stable, with a blood pressure of 140/80 mmHg and a heart rate of 80 beats/minute. She had no fever and no other abnormalities at the general examination. The neurological examination revealed: no clinical signs of meningeal irritation, no neck rigidity, wide-based gait, bilateral proximal muscle weakness in the lower limbs (4/5 MRC) accompanied by paresthesia in the same areas, globally abolished osteotendinous reflexes, and bilateral plantar flexion. A presumptive diagnosis of polyradiculoneuritis was established and differential diagnosis included myelitis, polyneuropathies, myasthenia gravis, Lyme disease, and even neuromyelitis optica (NMO) because in the earliest stages of the disease, the clinical presentation of

NMO spectrum disorder (NMOSD) can overlap or mimic other inflammatory diseases of the CNS (8). All the above mentioned were excluded by electromyography, lumbar puncture and clinical exam (for example, the patient reported no sensory impairment or painful spasms or visual disturbances which are known to be associated with NMO in 32% of the cases) (8). Lumbar puncture was decided, which revealed CSF glucose (91 mg/dl) and CSF protein (0.508 g/l) without pleocytosis. Other serology test results, including for hepatitis C virus (HCV), hepatitis A virus (HAV), human immunodeficiency virus (HIV), syphilis and Lyme disease, were negative. Under these circumstances, it was obvious that electromyography was necessary. Electromyography was performed on the same day in the Neurophysiology Department and highlighted: normal NCS on the cubital, radial, peroneal and sural nerves; markedly reduced distal motor response amplitude - 40% left peroneal muscle block. A significant MUAP dispersion was observed. F-wave latency was at the upper limit, with significant dispersion (Figures 1, 2). The tables below include all the tested nerves (Tables 1, 2, 3).

The patient's general condition gradually deteriorated: motor deficit worsened, the patient was unable to stand and walk, her spontaneous O2 saturation was 89%, which required her transfer to the Intensive Care Unit in order to start plasmapheresis.

After administration of the first dose of albumin, the patient experienced arrhythmias, marked dyspnea, hypotension (blood pressure 50/30 mmHg), bradycardia (heart rate 40 beats/min), symptomatology that partially remitted under cortisone therapy and adrenaline. The double plasma phase filtration procedure was initiated immediately. The patient underwent three sessions of double filtration, after which her clinical condition improved. EMG, lumbar puncture and clinical findings allowed reaching a final diagnosis: Guillain-Barre polyradiculoneuritis secondary to influenza vaccination.

Our patient started the rehabilitation program with a physiotherapist very early. This program included a complete range of motion and strengthening exercises necessary for mobility. Strengthening began in a gravity eliminated plane to allow repetitions without excessive fatigue. During this time, mobilization of the patient into sitting or out of bed to a chair was performed in order to promote pulmonary hygiene, circulation, and increase tolerance to upright postures. The rehabilitation program started with a Hughes scale score of 4, and after 21 days, a score of 2 was reached. The patient was recommended to continue rehabilitation in order to increase independence and safety with activities of daily living. Early initiation of a rehabilitation program can assist in preventing secondary complications, while later, therapists can assist with strengthening and increasing functional independence. In our opinion, a multidisciplinary team approach allows achieving the best outcomes for the patient.

Discussions

Monitoring for GBS following influenza vaccination remains important; enough evidence can be obtained to better understand the complex relationships between influenza, influenza vaccines, and the risk of GBS. There is sufficient evidence supporting an increased risk of GBS during the 6 weeks following receipt of seasonal influenza vaccine (1). As opposed to infectious causes, elevated protein levels (100–1000 mg/dl) appear in the CSF without an accompanying increased cell count (pleocytosis), as happened in our case (2).

In our case, it would have been helpful to co-administer IV immunoglobulins with double filtration, but the patient developed multiple allergies and side effects during the plasmapheresis session, which is why this possibility was excluded.

Rehabilitation should focus on proper limb positioning, posture, and orthotics. GBS patients frequently require psychological support, given the extremely disabling and frightening aspects of the condition and its sequelae (9). There is an increasing trend to use ultrasound in the management of pain. Knowing that ultrasound is one of the electrotherapy procedures applied due to its analgesic effects, muscle relaxing properties and massage, this might be used in the rehabilitation of patients with motor deficits (10).

Approximately 80% of patients with polyradiculoneuritis recover completely within a few months to one year; however, 5-10% of these patients experience one or more recurrences.

The particularity of the presented case is that the pathology appeared after vaccine administration, which is rarely reported in the literature.

Table 1.
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
right, Abductor digiti minimi, Ulnaris, C8 T1										
12	wrist	2,64	11,2	6,64	36,5	18	0,2	70		
	elbow	6,24	10,6	7,12	35,7	42	0,2	210	3,6	58,3
right, Abductor pollicis brevis, Medianus, C8 T1										
10	wrist	5,6	**8,09**	9,08	35,3	30	0,2	80		
	elbow	9,32	7,42	9,72	32,9	30	0,2	220	3,72	59,1
right, Abductor hallucis, Tibialis, l4 L5 S1										
2	sole of the foot	3,8	7,4	19,5	50,8	36	0,2	70		
	popliteal fossa	13,0	4,94	20,1	38,3	100	1	420	9,16	45,9
right, Extensor digitorum brevis, Peroneus, l4 L5 S1										
1	sole of the foot	6,99	3,16	18,5	22,1	48	0,2	70		
	head of fibula	15,7	**1,98**	16,9	14,2	56	0,2	340	8,68	**39,2**
left, Extensor digitorum brevis, Peroneus, l4 L5 S1										
5	sole of the foot	3,28	**9,74**	7,32	37,7	29	0,2	70		
	head of fibula	10,0	**5,7**	7,76	23,6	100	0,2	300	6,76	44,4

Table 2.
SENSORY CV

Test	Stimulation (recording) sites	Lat., ms	Ampl., µV	Dur., ms	Area, nV×s	Stim., mA	Stim., ms	Dist., mm	Time, ms	Vel., m/s
right, Ramus superficialis n. radialis, C5 C6										
9	1	1,48	12,0	0,96	6,1	17	0,1	80	1,48	54,1
right, n. Medianus										
8	wrist	4,88	2,8	1,32	2,0	17	0,1	140	4,88	**28,7**
right, n. Ulnaris										
7	wrist	2,08	5,2	2,36	6,7	25	0,1	120	2,08	57,7
right, n.Peroneus superficialis, L4-S1										
4	Middle third of leg	1,84	14,7	1,48	13,1	16	0,1	85	1,84	46,2
right, n.Suralis, S1-S2										
6	1	2,56	7,4	1,32	5,0	17	0,1	115	2,56	**44,9**

Table 3.
F-WAVE PARAMETERS

Test	Fmin lat., ms	F ampl., µV	M lat., ms	Fmin-M lat., ms	Fmean/M ampl., %	Max Vprox, m/s	V prox. diff., m/s
right, Abductor digiti minimi, Ulnaris, C8 T1							
13	26,2	661	2,6	23,6	4,0		
right, Abductor pollicis brevis, Medianus, C8 T1							
11	28,0	726	5,56	22,5	6,2		
right, Abductor hallucis, Tibialis, l4 L5 S1							
3	52,7	357	3,8	48,9	3,1		

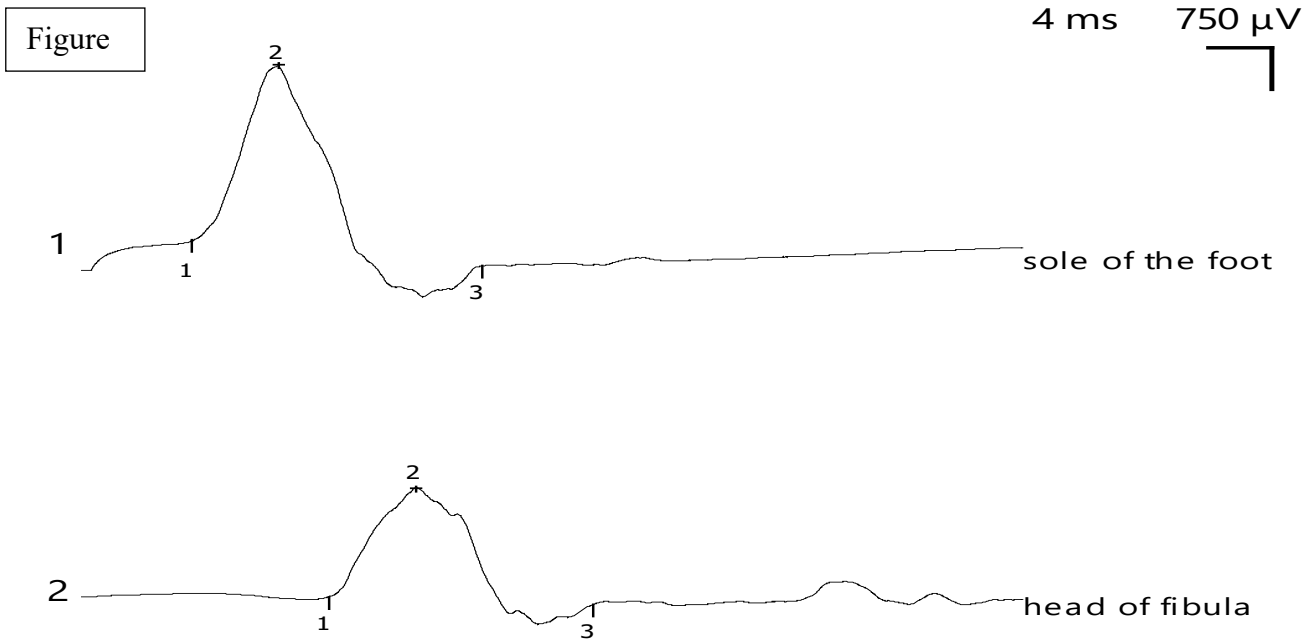

Fig. 1. Right, Extensor digitorum brevis, Peroneus, L4 L5 S1
M-wave amplitude with stimulation at the distal site 3.16 mV. Residual latency 5.2 ms. Velocity in the "sole of the foot – head of fibula" segment 39.2 m/s.

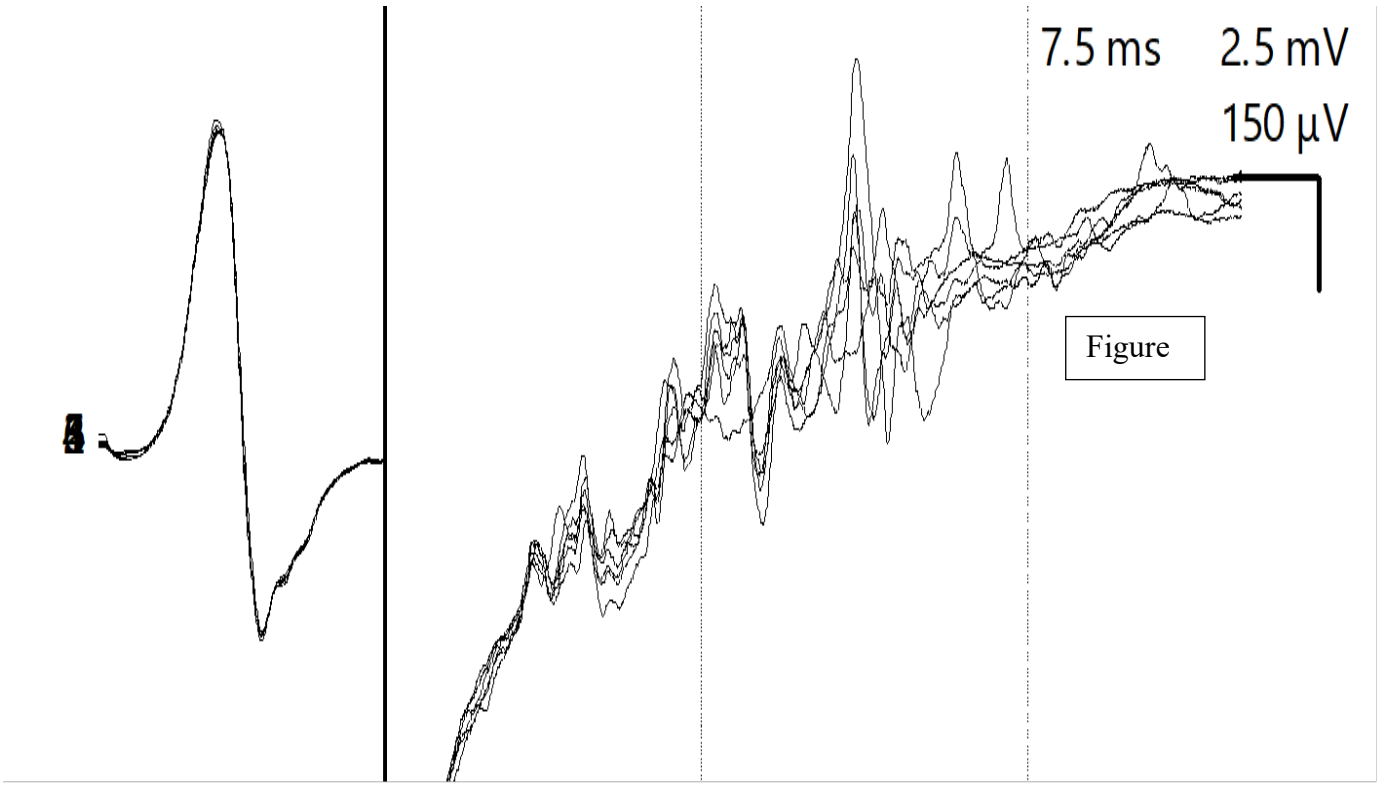

Fig. 2. F-WAVE Right, Abductor hallucis, Tibialis, L4 L5 S1. Min F-wave latency 52.7 ms, max 58.7 ms, mean 53.9 ms, difference 6.0 ms. Mean F-wave amplitude is 357 µV. F/M amplitude ratio: max 3.8%, mean 3.1%. No repetitive waves. No blocks, no gigantic waves. Peripheral latency 27.8 ms.

Conclusions

In our case, it was very important to recognize the neurological pathology. Neurological rehabilitation should be initiated immediately after immunological treatment has been completed (plasmapheresis).

Acute-phase rehabilitation for Guillain-Barre polyradiculoneuritis should include an individualized program of gentle strengthening, and manual resistive and progressive resistive exercises (11). Physiotherapists assist to correct functional movement, avoiding harmful compensations that might have a negative effect in the long run. There is also some evidence supporting the role of physiotherapy in helping GBS patients to regain strength, endurance, as well as to prevent contractures and bedsores (12).

All in all, we would like to highlight that the benefits of influenza vaccination outweigh the minor risks of post-vaccination GB syndrome.

Conflict of interest

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 this study.

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Non Cystic Fibrosis Bronchiectasis-new clinical approach, management of treatment and pulmonary rehabilitation

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Abstract

Non-Cystic Fibrosis Bronchiectasis (NCFB) are characterised by abnormal, permanently damaged and dilated bronchi due to the innapropiate clearence of various microorganisms and recurrent chronic infections.The diagnosis is suggested by the clinical presentation and is confirmed by multiple investigations. There are some comorbidities associated with bronhciectasis, such as chronic obstructive pulmonary disease (COPD), cardiovascular disorders, gastro-esophageal reflux disease (GERD), psychological illnesses, pulmonary hypertension, obstructive apnea syndrome(OSA). The condition has a substantial socioeconomic impact because it requests a multidisciplinary management and periods of exacerbations are common. The aims of the management of bronchiectasis are to reduce symptoms (such as sputum volume and purulence, cough and dyspnea), reduce the frequency and severity of exacerbations, preserve lung function and improve health-related quality of life. The multidisciplinary approach of bronchiectasis patients require along with the medical treatment, a specific plan of nonphamarcological strategies, including balneological intervention. There are a lot of techniques improving the airway clearence, such as: active cycle of breathing techniques (which include breathing control, thoracic expansion exercises, forced expiratory technique), oscilatting possitive expiratory pressure, autogenic drainage, gravity-assisted-positioning, modified postural drainage. Together with specific medication, these techniques can diminuate symptoms and improve the quality of life.

Key words: *NCFB, airway clearence, physiotherapy*,

Introduction

Non-Cystic Fibrosis Bronchiectasis (NCFB) is a chronic debilitating condition, first described by René Laennec in 1819. This condition is characterised by abnormal, permanently damaged and dilated bronchi, due to chronic bronchial inflammation because of inappropriate clearance of various microorganisms and recurrent or chronic infection (1). However, in a substantial number of patients no cause is found (2). Symptoms vary from intermittent episodes of respiratory infections with excessive mucus production to chronic symptomes with persistent daily expectoration of purulent sputum. It is a debilitating illness responsible for significant morbidity, with patients typically suffering from intermittent episodes of respiratory infections with excessive mucus production to chronic symptoms such as a persistent cough, daily sputum expectoration, recurrent chest infections and a poor health-related quality of life (3). The condition has a substantial socioeconomic impact because it request multidisciplinary management and periods of exacerbations are common (4).

Prevalence

Even if once NCFB was a very rare diagnosis, in the last two decades its prevalence has varied among populations and several studies have reported a prevalence ranging from 486 to 1106 per 100000 persons (5-7). The incidence of non-cystic fibrosis bronchiectasis is 2–5 patients per 1,000 population (8). It was observed that this pathology is more frequent in women and older individuals and many patients tend to have a more severe and symptomatic disease. Bellelli G et al. reported in one study of over 1,200 patients with bronchiectasis, 50% were over 65 years old and 19.1% were over 75 years (9). Increasing age is recognized as an independent risk factor for bronchiectasis severity (10). There is still a high incidence in developed countries and globally with the increased life expectancy of the general population, there is a greater risk of more people developing chronic illness, including bronchiectasis (11).

Patophysiology

The aetiology of NCFB is variable, but the common pathophysiological pathway represents a vicious cycle containing three important elements: inflammation, infection and damage on the bronchial wall. Potential causes of this breach include severe lower respiratory tract infections, gastric aspiration and/or inhalation of toxic gases, immunglobulin deficiency, ciliary disfunction, connective tissue disease, rheumatoid arthritis-related, airways disease (asthma/COPD), non-tuberculosis mycobacterium, foreign body inhalation, inflammatory bowel disease-relate. These modifications, through local or systemic inflammation, cause disturbances in the architecture of bronchial airways (12,13).

The usual mucociliary clearance defence mechanism is impaired, so the airways become chronically infected with a variety of bacteria which promotes further neutrophilic inflammation. Once the bacterial density in the airways is increasing, there is an exaggerated inflammatory response consisting of greater numbers of neutrophils and higher concentrations of neutrophil degradation products beside other inflammatory markers (14).

So, the patient with NCFB is enrolled in a vicious cycle of infection and inflammation developing persistent symptoms, frequent exacerbations and further airway damage (15). These modifications such as host inflammatory response and microbial cytotoxins, cause additional structural damage of the lung and further impair mucus clearence, so it is easier for the microorganisms to form biofilms (16). The role of the biofolms is to protect the bacteria from the clearence of the host immune system which reduce the effects of antibiotics further potentiating airway inflammation (17).

Clinical Presentation

Non-cystic fibrosis bronchiectasis can be presented as asymptomatic, or in some individuals can cause massive haemoptysis and respiratory failure, so the most common clinical presentation is between these extremes. In one study of 103 adults with NCFB, 98% reported a chronic cough, and 76% of patients had daily sputum production. From common presenting symptoms, dyspnoea occured in 62% of cases and chronic fatigue was reported by 74% of subjects (18,19). Moreover, intermittent haemoptysis occurred in 26-51% of cases, which at times became life-threatening (19). On the other hand, many patients with bronchiectasis require frequent hospital admissions for recurrent pneumonia(18) and depression or anxiety which may significantly affect their quality of life (20).

Investigations

Physical examination and history contribute to the diagnosis of bronchiectasis.The most common modifications include crackles (73% of subjects), rhonchi (44%) and wheezing (21%-34%) (18).

The first tool to evaluate a patient with bronchiectasis is a standard chest radiography which can detect multiple areas of bronchial wall dilatation in subject with moderate to severe bronchiectasis. However, studies have evidenced that chest radiography has moderate sensitivity(88%) and poor specificity (74%) for the detection of bronchiectasis (21).

The current gold standard for the diagnosis and confirmation of bronchiectasis is high-resolution computed tomography(CT). The characteristic feature of NCFB by CT is bronchial wall dilatation with the luminal diameter greater than 1-1.5 the size of the accompanying pulmonary artery branch. Other findings include absence of normal tapering of the bronchi, bronchial wall thickening, mucoid plugging of the airways and proximity of visible airways close to the pleura (22).

On the other hand, pulmonary function testing is often used to evaluate the subject with chronic pulmonary diseases. Patients with bronchiectasis usually present mild to moderate airway obstruction, with a forced expiratory volume in the 1st second (FEV1)/forced vital capacity (FVC) ratio less than 70 and a FEV1>50% of predicted. In 22% of cases with NCFB, there is a significant bronchodilatator response(18). Some conditions are associated with more severe obstruction, such as: a history of Pseudomonas infection or colonisation, multilobar involvement of disease, greater purulent sputum volume and those patients with at least four exacerbations over a 2-year period (23).

In addition, sputum culture must be obtained from all patients with bronchiectasis. The most common organisms initially isolated are Gram negative bacteria including Haemophillus infuenzae (47%), Pseudomonas aeruginosa (12%) and Moraxella catarrhalis (8%). After a period of time, Pseudomonas aeruginosa becomes more frequent. All in all, Gram-positive bacteria such as Streptococcus pneumoniae and Staphylococcus sureus are rare (24).

In the last decades, Non-tuberculosis mycobacterium (especially Mycobacterium avium) incidence has increased accounting for 2-30% of pathogens isolated (25).

Once bronchiectasis is confirmed based on clinical presentation and radiographic imaging, determining the underlying cause is important to effective therapeutic management. First of all, both primary and secondary immunoglobulin deficiency (in particular IgG deficiency) should be tested because it can be associated with bronchiectasis and the frequency of infections can often be reduced by immunoglobulin replacement therapy. All patients should undergo testing for allergic bronchopulmonary aspergillosis(ABPA), depending on radiological features (temporary infiltrates are seen initially and it can eventually lead to proximal bronchiectasis) and tests to confirm aspergillus hypersensitivity (raised peripheral blood eosinophils, total IgE, Aspergillus specific IgE or positive skin test with or without aspergillus precipitins) (26).

Comorbidities

The possibility of coexisting inflammatory bowel disease, connective tissue disease or vasculitis. Comorbidities are more likely in the elderly and clinical suspicion will warrant relevant screening such as ANCA, anti-CCP, fecal calprotectin etc. Bronchiectasis associated with a connective disease such as rheumatoid arthritis is often more aggressive and carries a worse prognosis (26).

In addition, several other pathologies may occur at any stage of bronchiectasis and are likely major contributors to increased hospitalisations, healthcare utilisation and socioeconomic costs (27).These include COPD, cardiovascular disorders, gastro-esophageal reflux disease (GERD), psychological illnesses, pulmonary hypertension, obstructive apnea syndrome(OSA), cognitive impairment, lung, oesophageal and hematological malignancies (20,28-29). One of the important comorbidities is OSA, but the relationship between sleep disorders and bronchiectasis has not been well described. There is a assumption that, due to the irreversible dilatation of the bronchi, the presence of secretions, and airflow obstruction, patients with non-cystic fibrosis bronchiectasis may be predisposed to hypoxemia during sleep, or to symptoms that may lead to arousal (30).

The importance of screening programs for comorbidities, such as OSA and diabetes mellitus type 2 is evident in bronchiectasis patients, moreover because some studies showed that only being overweight itself produces a greater risk of developing a metabolic syndrome and sleep disorders (31).

Management

The aims of the management of bronchiectasis are to reduce symptoms (such as sputum volume and purulence, cough and dyspnea), reduce the frequency and severity of exacerbations, preserve lung function and improve health-related quality of life.

In the multidisciplinary management, every respiratory phisician must take into account the gravity score. There are several scales of severity. One of them is the one proposed by Chalmers et al. who introduced the bronchiectasis severity index (BSI), including High resolution Computed Tomography (HRCT) score, FEV1, Medical Research Council dyspnoea score, bacterial colonisation (Pseudomonas aeruginosa or other pathogenic bacteria), prior hospital admission and exacerbations. They conclude that the BSI was a sensitive tool in predicting future risks of hospitalisation(10). On the other hand, Martinex-Garcia et al. (32), established the FACED score, a simpler one, which includes FEV1, age, Pseudomonas aeruginosa colonisation, radiological extension and dyspnoea. Similarly, the FACED score effectively predicted mortality.

The first step of the management is the patients' education; they should understand the diagnosis in order to limit other injury to the airways, by smoking cessation, limiting infective insults, prevention of viral infections by receiving the annual seasonal influenza vaccination (33-34). Also, in obese patients, diet is one of the most important interventions along with a training program in order to reduce body mass index (BMI), improve sleep quality and increase respiratory muscle endurance in patients with bronchiectasis and other comorbities, such as OSA, but in selected cases with associated craniofacial deformities, early orthodontic treatment could be necessary (35,36,37). Also, weight loss improves the cardiovascular status, moreover because obese patients develop a metabolic syndrome which can be fatal for bronchiectasis patients because it can reduce their effort capacity and their quality of life (38).

The multidisciplinary approach of bronchiectasis patients requires along with the medical treatment, a specific plan of nonphamarcological strategies, including balneological intervention: an active cycle of breathing techniques (which include breathing control, thoracic expansion exercises, forced expiratory technique), oscilatting positive expiratory pressure, autogenic drainage, gravity-assisted-positioning, modified postural drainage.

Airway clearance

Airway clearance techniques (ACT) are nonpharmacological strategies used worldwide in order to improve symptoms, reduce exacerbation frequency and increase quality of life (39). There are some short terms goals of ACT such as more effective sputum clearance which has been proven to improve ventilation, reduce cough impact and breathlessness. On the other hand, its long-term effects are reducing airway damage by stopping the vicious cycle of colonization and subsequent inflammation, reducing the number of exacerbations and hospitalizations and improving the quality of life (40).

ACT are a key component in the management of patients with bronchiectasis, moreover for patients with a chronic productive cough or difficulty expectorating sputum which may benefit from regular twice daily ACT as recommended in the current guidelines (41). Active Cycle of Breathing Technique (ACBT) is a repetitive cycle consisting of 3 distinct components: breathing control (BC), thoracic expansion exercises (TEE), and the forced expiration technique (FET). The cycle and length of each component are flexible and can be adapted to individual needs. BC is relaxed tidal breathing using the lower chest and performed at the patient's own rate. Its role is to minimize any flow obstruction. TEE are dynamic procedures and are performed by taking deep slow inspirations through the nose (if possible), followed by an inspiratory pause with an open glottis, and subsequently relaxed expiration, in order to mobilize the secretions. The FET is a principle component of the ACBT and is defined as a combination of 1 or 2 forced expirations (huffs) interspersed with periods of BC. The lung volume can be varied depending on which segment to target. For example, FET from high lung volumes helps to clear secretions, whereas FET from low lung volumes helps to mobilize secretions. The FET aims to move the mobilized secretions to the proximal airways to be cleared, which then may subsequently require a cough (42). However, in practice ACT remains underutilized, as showed by The European Bronchiectasis Data Registry (EMBAC) that reported that only 45% of patients perform ACT regularly (43,44). ACT has two main principles: to ventilate the regions distally, behind the obstruction and to modulate the expiratory airflow to propel secretions proximally up the airways. So, to enhance the mucus clearance, the peak expiratory flow rate should be at least 30-60 l/min and greater than the inspiratory flow (44). Other techniques used in patients with bronchiectasis are: oscilatting positive expiratory pressure (PEP), autogenic drainage (AD) and ELTGOL (active technique where the patients carries out slow expiration with the glottis open in a lateral decubitus position).

PEP uses a set resistance that is applied throughout expiration to enhance the mobilization of secretions, by using either a mask or a mouthpiece attachment and induces a temporary increase in functional residual capacity. Moreover, it facilitates collateral ventilation, and encourages the recruitment of closed airways. Furthermore, it may splint airways open, aiding expiratory airflow, because airways are often prone to collapse during active expiration as a result of increased intrathoracic pressure (45,46). Autogenic drainage (AD) is a 3-phase breathing programme using high expiratory flow rates at varying lung volumes to facilitate mucus clearance. It requires a progressive volume increase in order to maximize expiratory flow velocity to produce shearing forces and move secretions. Inspiration should be low flow with an inspiratory pause and open glottis. Expiration should be a higher flow, although aiming to minimize airway collapse (47,48).

Considering the studies, Patterson et al. demonstrated that ACBT versus oscilatting PEP had no improvement in lung function or sputum weight over a 10–14 day treatment period in 20 stable patients (49). This idea was sustained in the study of Thompson et al. who also took into consideration the quality of life, which was not improved after a 4-week treatment period (50). In a study performed by Herrero Cortina et al., both AD and ELTGOL resulted in significantly greater sputum compared to the control group (51). Anther study, involving ELTGOL, made by Munoz et al. which compared the ELTGOL technique to placebo exercises twice daily in 44 patients over a 1-year period, reported fewer

exacerbations, reduced cough impact and improvement in the quality of life in the therapy group (52).

Another technique is gravity-assisted positioning (GAP) which is passive and relies solely on the effects of gravity and changes in regional ventilation with positioning, so it cannot be used alone as an ACT. Patient position themselves to drain specific lobes within the lungs, using gravity to enhance movement of secretions. For example, the lower and middle zones of the lung drain includes a head-down tip position. Studies showed that the performance of ACTs in GAP positions may help enhance sputum clearance (53). Modified postural drainage (MPD) uses similar specific lobar drainage positions as in GAP, but eliminates any head-down tip, thus using gravity neutral positions. MPD is recommended in patients that have contraindications for GAP, for examples in subjects which are associated with GORD. Cecins et al assessed the effectiveness of modified positions without a head-down tip and showed no significant difference in MPD versus GAP, because the results of sputum weight did not vary more than 15% (54).

These studies with interventions longer than a single treatment demonstrate some proof of the concept on the effectiveness of ACT in bronchiectasis and support the general consensus that currently no one ACT is superior in terms of clinical outcomes (55). There is wide variety of techniques that are age, preference and co-morbidity dependent, so the selection of ACT should be targeted according to the patient's individual characteristics (56). Taking into consideration the comorbidities, such as OSA, the airway clearance is very important because the presence of various microbiological and inorganic structures on the inner surface of CPAP masks and tubes emphases the risk of microbial and inorganic elements inhalation into the upper and lower airways. Therefore, the microclimate and the hygiene of CPAP device, including masks and tubing is very important in order to reduce exacerbations (57-58). Also, patients with bronchiectasis should reduce their exacerbation risk by limiting air pollution both indoor and outdoor and the exposure to allergenics (59).

Airway humidification

The aim of airway humidification (with molecular water added to gas) is to reduce mucus viscosity and enhance flow through the airways. There are a few studies on this subject, which demonstrated that airway humidification increases airway clearance and sputum yield, so can be used in addition to ACT. However, the evidence is insufficient to recommend it for routine use in subjects with bronchiectasis (60).

Mucoactive therapy

Studies showed that mucoactive therapy should be considered if ACT are not effective (41). Mucoactive medications potentially increase the ability to expectorate sputum and/or decrease mucous hypersecretion and should be coordinated with ACT to ensure the overall effect is optimized. As Balsamo et al. showed, they can broadly be characterized into several major groups based on their potential mechanism of action (61):

1. Expectorants are drugs that induce discharge or expulsion of mucous from the respiratory tract. Typically, this requires a coughing action to loosen and bring up the mucous from the lungs or upper respiratory tract. Examples include hypertonic saline (HTS) and a solution of manitol.
2. Mucoregulators: drugs that regulate mucous secretion or interfere with the DNA/F-actin network. Examples include carbocisteine and anticholinergic agents.
3. Mucolytics: drugs that decrease mucous viscosity. Examples include N-acetylcysteine, erdosteine and DNase.
4. Mucokinetics: drugs that increase mucociliary clearance by acting on the cilia. Also referred to as cough clearance promoters. Examples include bronchodilators and surfactants (61).

The European Respiratory Society (ERS) guidelines (62) summarize the findings of three systematic reviews that have comprehensively examined the current evidence for mucoactives (63-65). It was proven that none of the mucoactive agents significantly reduced the number of exacerbations, but one trial with 88 participants showed that high doses of bromhexine with antibiotics significantly eased difficulty in expectoration and sputum production days compared to a placebo (66). HTS action is achieved by altering the concentration of water in the mucus but, clinical trials are limited. However, it was evidenced that it is responsible for yielding greater sputum weights with greater ease and less viscosity (67). The manitol role is to enhacemucocilliary clearance with improved mucus

clearance for up to 24 hours after inhalation and it was demonstrated that it has an important positive effect on small airways function, cough tansportability and health-related quality of life (68). The prescription of mucoactive therapies should be done in addition to ACT and therefore it is important that the mechanism of action of mucoactive drugs and their timing with ACT are taken into consideration. In case of HTS which has a short-term/immediate effect, the ACT should be done immediately after HTS inhalation (69). There are two active clinical trials exploring the efficacy of commonly used mucoactives (HTS and carbocisteine) in bronchiectasis. The results are likely to have an important impact on future practice (70-71), moreover because there is stronger evidence for carbocisteine and HTS in other conditions and these are the most commonly usedmucoactives in bronchiectasis (72). Regarding inhaled mucolytics, their role is to cleave the excessive quantities of DNA accumulated due to neutrophil activity, reduce sputum viscosity, improve expectoration, airway clearance and lung function. However, it is not recommended in routine use because of its side effects with the decline of FEV1, higher rate of exacerbations, increased use of antibiotics and a greater rate of hospitalisations (73). On the other hand, inhaled corticosteroids are recommended to be used in the treatment of bronchiectasis together with rehabilitation programmes where there is co-existing obstructive airways disease such as asthma, COPD or ABPA (74).The British Thoracic Society (BTS) bronchiectasis guidelines recommend a trial of bronchodilator therapy if shortness of breath affects the patient's activities of daily living. In these situations it is worthwhile to perform a trial of short-acting beta-agonist (SABA) or short-acting muscarinic-antagonist (SAMA) initially and if there is clinical benefit then proceed to a long-acting bronchodilator (75).

Antimicrobial therapy

The number of clinical trials investigating antibiotic therapy in NCFB is small, but has been administrated systemically or via inhalation (76). However, chronic treatment is not recommended and the most effective antibiotics are macrolides. They act with an anti inflammatory effect, reducing the total bronchoalveolar lavage cell count, sputum volume and interleukine 8 and neutrophil activity. Also, Anwar et al. showed an improvement in exacerbation frequency, spirometry and sputum microbiology when treated with azithromycin 250 mg three times a week (77). However, inhaled antibiotics have more limited side effects, but may be less tolerated because of the bronchospasm. For example, inhaled tobramycin decreased the number of admissions and days in the hospital and it has been showed that by prolonging their use may appear a positive effect. Also, there are continuous improvements in drug design, with aerolised formulations that are well tolerated by the epithelial surface, able to penetrate infected sputum and capable of avoiding immune system clearance in order to achieve a better therapeutic response (78).

Pulmonary rehabilitation

Pulmonary rehabilitation, with patient-centred exercise training and collaborative self-management education delivered by an interdisciplinary team and centred on the specific needs of the patient (30), has evolved beyond the confines of chronic obstructive pulmonary disease (COPD) management. Pulmonary rehabilitation must take into account the patients' comorbidities. In general, PR incorporates several exercise modalities (treadmill walking, cycle ergometry, weight lifting and arm ergometry) and patient education and works through secondary impairments such as peripheral muscle dysfunction, psychosocial dysfunction and maladaptive behaviours (79). It is necessary that patients be educated once the pulmonary rehabilitation programme is initiated to minimize their exposures to respiratory irritants. In this direction, smoking cessation is crucial in addition to the avoidance of air pollution, boot outdoor and indoor (radon exposure) (80,81,82). Exercise training (ET) programmes are comprised of the exercise modalities without an educational component. PR and ET programmes are generally aimed at improving both upper limb and lower limb endurance and are tailored to the needs of the individual patient. The location of the programmes vary: some are incorporated into hospital-based physical medicine and rehabilitation medicine facilities; others are free standing and may even be in a community centre or in an outpatient physiotherapy department. Based on the location of the exercises, the trained stuff may include: exercise physiologists, respiratory care practitioners, physiotherapists and nurses. Also, the patients participating in PR or ET are generally monitored

with oximetry and occasionally cardiac monitoring. The duration of the programs vary: in the United States, these programmes are generally comprised of an initial intensive phase which includes 36 1-hour sessions over 12 weeks followed by a selfguided maintenance phase, but in other parts of the world, the patients may receive shorter or longer periods of supervision (79).

A recent systematic review confirmed the short-term benefits that patients achieve from participating in supervised PR and ET, but noted that sustaining benefit is challenging (83). However, the study of Ong et al., suggested that despite the absence of a structured maintenance program, the 6-minute walking distance remained significantly higher than baseline at 12 months and the chronic respiratory disease questionnaire (CRQ) scores similarly remained stable for 12 months (84). In addition, Newall et al. which conducted the first study to assess the effects of exercise training in patients with bronchiectasis showed that an 8-week PR program was effective in improving the exercise capacity and health status, regardless of the addition of inspiratory muscle training (85). Moreover, Mandall et al., in one study comparing PR and chest physiotherapy versus chest physiotherapy alone in 30 patients with bronchiectasis, observed short-term improvement in PR outcomes, with a reduction in the frequency of exacerbation after 12 months, as well as an improvement in the walking distance (86).

The physiological rationale for PR and ET in bronchiectasis is that muscle weakness and physical inactivity may play a role in disease progression as well as impact the quality of life, frequency of infectious exacerbations and the ability to mobilize secretions (87). One observational study of 41 patients with bronchiectasis showed that PR significantly improved forced vital capacity and residual volume measurements (88). Lee et al, concluded in one study that compared ET with airway clearance training to standard care that there was an improvement in exercise capacity, dyspnoea and fatigue as well as fewer exacerbations over 12 months (89). Patients that cannot perform ET, can benefit from neuromuscular electrostimulation (NMES) which has been extensively used as a technique to improve muscle function and structure in different areas of rehabilitation and sport training programs (90).

Conclusion

Non cystic fibrosis bronchiectasis is a chronic, inflammatory lung disease that is characterized by a chronic cough, daily sputum production, and frequent exacerbations. There is a spectrum of disease, ranging from minor symptoms to a severe and progressive condition that can result in overwhelming infection or respiratory failure. It has become increasingly recognised that treatments for bronchiectasis cannot be extrapolated from other chronic respiratory diseases and more studies are required both to better understand the disease pathogenesis and to establish the optimum multidisciplinar approach to the management of this debilitating disease. Pulmonary rehabilitation is a comprehensive and effective treatment approach that improves overall clinical status and increases the level of physical activity in patients with bronchiectasis. It is essential that patients with bronchiectasis are included in comprehensive PR programs that are planned based on the patients' current clinical status and individual needs, in order to increase their quality of life.

Conflict of interest

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

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How do I track Cardiac Rehabilitation in my patient with ischemic heart disease using Strava

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Abstract

Cardiac rehabilitation is a program which reduces morbidity and mortality in patients with ischemic heart disease. However only some European centers provide these programs for patients diagnosed with cardiac ischemia. Therefore home-based programs were developed for cardiac rehabilitation. Strava is a social network developed to track activities of running and cycling both in athletes and individuals searching for recreation and sport activities. In our work we present an approach based on Strava tracking to improve the quality of cardiac rehabilitation. Real-time monitoring of heart rate, steps per minute and speed during recreational or competitive activities can be used to increase physical capacity in individuals with ischemic heart disease.

Key words: *cardiac rehabilitation, Strava, ischemic heart disease, home-based*,

1 Introduction

Cardiac rehabilitation is the sum of actions needed to provide an optimal level of physical activity after an acute episode of cardiac disease. Beside risk factors, physical exercise is the cornerstone of rehabilitation (1).

1.1 Cardiac rehabilitation in ischemic heart disease.

Patients with acute coronary syndrome or post-PCI have a class I level A indication for cardiac rehabilitation in current guidelines, and patients with chronic angina have a class I level B indication (2). Physical training has been shown to reduce risk factors in patients with ischemic heart disease (3). Patients that had an acute myocardial infarction or an acute coronary syndrome, or underwent a coronary bypass procedure are eligible for cardiac rehabilitation programs. If the patient already developed NYHA IV heart failure or the coronarography shows significant remaining lesions or significant ventricular arrhythmias, cardiac rehabilitation could be postponed or even excluded as a way of treatment (4).

1.2 Phases of Cardiac rehabilitation in ischemic heart disease.

Cardiac rehabilitation programs consist of 3 phases. The first phase starts early after stent implantation, or medical treatment, in hospital, after assesing the basic functional mobility of the patient and associated risk factors. Upon discharge the patient can continue phase 2 consisting in monitored excercise activities. The last phase is phase 3 with increased intensity of excercise guided by self- monitoring of the heart rate, cadence, and pace and self-perceived exertion (5,6).

1.3. Heart rate during physical training.

Patients after an acute coronary event have an accelerated heart rate increase to standardized workload, similar to individuals with prolonged bed rest. This is called a deconditioning response to disease. The cardiac response to excercise is related to a decrease in the vagal tone which is further translated to an increase in the heart rate (7). During dynamic tpes of exercise heart rate increase is liniar to workload and within minutes it reaches a steady state for a given intensity of physical activity. Heart rate during excercise depends on the age of the patient, body position, type of physical activity, environment, and can be measured using different devices or apps (fig 1,2).

Fig. 1. Garmin Forrunner device used for excercise tracking. It can display distance, heart rate and pace. It uses an optical heart rate sensor with green light on the back of the device to measure heart rate.

Fig. 2. Polar device used for excercise tracking. It has a pectoral belt for heart rate measurement that transmits the signal to the watch using bluetooth technology.

2. Devices for home-based rehabilitation.

Phase 3 rehabilitation is an alternative to cardiac rehabilitation programs that take place in hospitals or as out-patient rehabilitation. Home based rehabilitation may be improved using devices that measure not only biological variables such as heart rate, blood pressure, respiratory rate and caloric count but also cadence, speed and distance using motion sensors and accelerometers with long-term information storage programs. All those devices increase the adherence of patients to cardiac rehabilitation programs. A high number of devices for home-use are launched and improved every month to increase the ease of access to remote monitoring. It is possible in our days to assess home- based cardiac rehabilitation with real-time remote monitoring using various apps and devices making the follow-up of patients more efficient (8).

Polar and Garmin devices are tools for exercise tracking that can be used for home-based cardiac rehabilitation programs. They can be used by cardiologists to evaluate their patient's activity and keep track of the progress during the excercise program. Both Garmin and Polar devices include a wide range of watches of various size and style with or without an attached chest band for respiratory and heart rate monitoring during exercise. Devices can monitor physical activities like walking, running, swimming, bike riding and much more (9).

2.1 Strava platform

Strava platform has an important role in the quality of the rehabilitation program and patient's adherence. Doctors can obtain information both during excercise and postexcercise: activity duration, speed, average pace, elevation gain, calories burnt as well as heart rate and respiratory rate at specific splits during excercise, related to distance, pace and elevation. Strava automatically processes diagrams and figures based on measured parameters. This makes cardiac rehabilitation significantly easier for the patient and user friendly for the doctor that supervises the program from the hospital or his own computer (10).

Another important asset that this platform provides is the social network interface that can help increase the adherence to the program by offering the possibility to join various running clubs even cardiovascular rehabilitation clubs which can offer further support and motivation for the patient.

2.2. Individual coaching by telephone or internet

The telehealth or e-health technologies due to their lower grade of flexibility and professional input on excercise programs may not be as effective as the phase II-hospital based rehabilitation program. Nevertheless, the results of remote excercise monitoring can be improved by the real time advices of a cardiologist during the rehabilitation program, by phone, email or phone messages using different applications. Interaction with a cardiologist is expected to increase both the patient's adherence to the program and quality of training (11).

3. Stepwise approach to Strava tracking

Step 1: Before beginning stage 2 of cardiac rehabilitation a stress test should be performed to assess the maximum heart rate during physical activity. If the test is not performed the theoretical maximum heart rate will be calculated using the formula 220-age.

Step 2: The patient's risk factors will be assesed: low-risk, high-risk or very high-risk. High-risk patients are considered those with ejection fraction of < 40%, patients with failed reperfusion therapy, patients with severe three-vesel disease and those > 70 years old. Very high-risk patients are considered those that already have clinical signs of heart failure NYHA III of IV.

Step 3: The patient should aquire a Strava compatible tracking device: Garmin, Polar (fig 1,2), Suunto, Tomtom, Fitbit and synchronize the device with the Strava personal account.

Fig. 3. Map with the distance traveled by the patient. The GPS system of the Garmin or Polar watch can trace the patient while exercising. (Source: personal collection)

Fig. 4. After terminating the daily training program, the patient can upload his activity on Strava. This image shows the pace curve as minutes/km during the total duration of 50 minutes training.
(Source: personal collection)

Step 4: The cardiologist will establish thre excercise intensity according to the risk, using the Karvonen formula:

Low risk = 0.6 x (max heart rate-resting heart rate)+resting heart rate.

Hish risk=-0.5 x (max heart rate-resting heart rate)+resting heart rate.

Very hisgh risk = 0.4x (max heart rate-resting heart rate)+resting heart rate.

Step 5: The patient will start training with a frequency of 4 times/week for 30 minutes then will increase gradually to 7 times/week and up to 1 hour.

Step 6: Each time the patient performs physical activity, information will be uploaded to Strava and can be seen by the cardiologist for further advices.

Step 7: The cardiologist can check the activities uploaded by his patients from his office or from his own home. He will search for: distance traveled by the athlete, speed, cadence and heart rate, different graphs and maps (Fig 3-6).

Step 8:

After verifying the data provided by Strava platform, the doctor can give advices on how to increase or decrease distance, speed and frequency of activities/day.

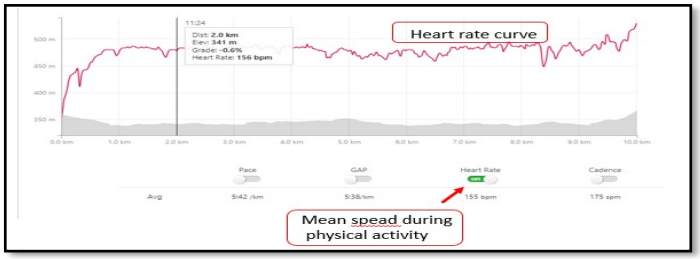

Fig. 5. Heart rate curve. For a rehabilitation cardiologist this curve is very important as it shows the intensity of physical activity performed by the patient. The patient did more intense activity than calculated by the Karvonen formula: for a 40- year-old patient is: (180-80) x 0,6+80=140 bpm.
(Source: personal collection)

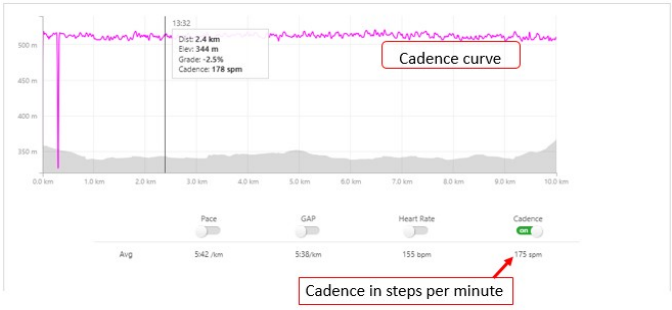

Fig. 6. Cadence curve. The figure shows the number of steps the patient takes per minute. In this case 175spm is a good cadence. (Source: personal collection)

Conclusion:
Exercise training remains the cornerstone of rehabilitation in cardiovascular patients as it decreases morbidity and mortality in patients with ischemic heart disease, it improves symptoms and cardiac risk factors, as well as increases the quality of life by increasing physical functioning and exercise capacity. Strava, as a social network, using Polar and Garmin tracking devices, helps the patient with ischemic heart disease by improving the quality of the rehabilitation and increases the adherence to home based cardiac rehabilitation program

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

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Pharmacological pain management in patients with chronic hepatic disease

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Abstract

The liver has a central role in the pharmacokinetics (absorption, distribution, elimination, etc.) of drugs. With hepatic insufficiency, the metabolism of drugs decreases, which accumulates metabolically or toxic active products. Some medicines can aggravate a pre-existing liver disease. Medicines used in this group of patients (especially diuretics and centrally acting preparations) can often cause impaired renal function or hepatic encephalopathy. The general principles of assessment, pain management and analgesia should be prescribed taking into account the Word Health Organization (WHO) recommendations for these patients, with careful and frequent monitoring of patient progress during treatment administration.

Key words: *hepatotoxicity, hepatic dysfunction, cirrhosis, pain medication*,

1 Introduction

Recent decades have led to an increase in the prevalence of chronic illness in general, with the impact being felt at the level of quality of life. Among the liver diseases, pain is one of the most common reasons why patients are addressing medical services, with a frequency ranging from 17-24% in cases of cirrhosis to 67% in those with chronic viral hepatitis C (1). Unfortunately, this symptom is poorly understood, difficult to approach and often has inappropriate treatment. Repercussions can be summed up by a change in the quality of life for this group of people (2). Recent data suggests that pain is related to psychiatric symptoms, race and progression of dysfunction rather than to the etiologic factor of hepatic impairment (3).

The primary fear for practitioners is related to the risk of hepatotoxicity and accumulation of toxic metabolites of pain medication, requiring knowledge of pharmacokinetic details along with the profile of their side effects. In principle, for patients with a mild degree of hepatic impairment, the antialgic therapeutic palette is the same as that is used with people who have no liver disorder. Susceptibility to the onset of side effects increases with the impairment of hepatic function, with changes in the pharmacokinetics and hemodynamics being incriminated (4).

There are a number of so-called "classical" tests to evaluate liver function, taken from the blood (serum transaminases, bilirubin, alkaline phosphatase, prothrombin time, albumin), but they do not really appreciate "how well it works" or not. Good, modified values may have extrahepatic etiology, or values may be within normal limits even if patients experience an advanced stage of hepatic impairment. More targeted tests have been developed to quantify the ability of the liver to transport organic anions or drug metabolism, such as green indocyanine clearance, but use in clinical practice is rare (5, 6).

The reluctance to administer antialgic medication in patients with hepatic pathology may be justified in part because of the lack of a clear limit of liver function from which a dose adjustment or choice of a different preparation is required. As a general rule, patients with severe impairment (decompensated fibrosis or cirrhosis) need to modify dosages especially for those with portal hypertension or renal insufficiency. Exceptions include active alcohol or polypragmazia, where severe hepatotoxicity of concomitant paracetamol can occur regardless of the stage of hepatic disease (7, 8).

Correlation between liver dysfunction and physical function has not been rigorously investigated. A study has highlighted the presence of a motor deficit at Child-Pugh scores ≥6. It is assumed that the mechanism of appearance resides in poor muscle protein synthesis encountered in liver dysfunctions. The results support the idea that this category of patients has a higher risk of developing sarcopenia, which by extrapolation recommends developing a physiotherapy program taking into account the Child-Pugh score (9).

This article proposes a review of the most used pain medication and anti-rheumatic drugs in patients with coexisting liver disease. In the search we used as liver terms "dysfunction", "failure", "impairment", "insufficiency" and separate hepatic cirrhosis. Most of the existing studies have small sample size, with no placebo group or case studies or expert opinion. In many situations, "cautious use" is found not only in the medicine leaflet, but also in published case studies. The recommendation of the authors is to monitor liver function and to know the pharmacokinetics of the drug. Another important aspect is the pathological context in which anti-rheumatic pain medications are administered: most patients with liver disease have a series of comorbidities (renal, cardiovascular disease) that prevent or contraindicate the administration of some drugs. Also, co-morbidities require other types of treatments that interfere with antialgic drugs, which further restrain therapeutic benefits. The following list of pain medication takes into account the WHO pain treatment leader (stage I-II-III).

ANALGESICS

• STAGE I

1. PARACETAMOL:

Because of its good safety profile along with the absence of sedation or nephrotoxicity, it is the pain medication of choice for patients with hepatic impairment under the recommended dosage (4). It should be noted, however, that about half of the overdose cases occur accidentally, given that many over-the-counter products are combined drugs also containing paracetamol (10).

The frequent recommendation for cirrhotic patients with advanced liver disease or alcohol users is not to exceed 2 g/day (11, 12). For those with severe alcoholic liver or acute liver dysfunction, paracetamol should be avoided (10).

2. NON-STEROIDIC ANTIINFLAMMATORY DRUGS (NSAIDs)

Their systemic administration is not recommended for patients with cirrhosis or severe chronic liver disease (including aspirin). Topical products may be considered as a therapeutic option. However, more studies are needed on their safety profile (there is some degree of systemic absorption and it is assumed that this would not suppose to increase any risks for those patients with cirrhosis).

These restrictions are explained by several mechanisms: inhibition of prostaglandin production with aggravation of hydrosaline retention and implicit ascites, increased risk of gastrointestinal haemorrhages (varicose and non-varicose) due to thrombocytopenia and precipitation of acute renal insufficiency (approximately half of the patients with cirrhosis present concomitant kidney damage leading to increased likelihood of toxicity) (3, 13).

• STAGE II

The use of opioids is controversial as the liver is the main site for their metabolism. In liver disease, the clearance of drugs can be low and/or because of the decreased metabolism during oral administration the first liver passage can be fast (3). In the case of long term opioid consumption, tolerance should be considered, which implies a dose escalation, implicitly a higher risk for the development of hepatic encephalopathy (4).

1. CODEINE

It is a weak opioid, a precursor drug and its analgesic effects being installed only after conversion to morphine via CYP2d6. In hepatic impairment, the intensity of analgesia is diminished or even absent because of the decrease in the oxidation capacity of this enzyme. At the same time, diminished clearance of codeine should be taken into account, which may lead to accumulation of the drug and, implicitly, to depressed ventilation (4). There are, on the other hand, "fast/ultra fast" metabolizers. In these patients, morphine conversion of codeine occurs rapidly, reaching higher plasma concentrations of morphine; they are much more predisposed for developing adverse reactions even for common doses (14).

The recommendation is to choose other therapeutic alternatives (13).

2. TRAMADOL

It is a centrally acting synthetic compound that is oxidized at the liver in the active metabolite - O-desmethyltramadol (M1), which is metabolized by CYP2D6, and its antialgic properties are therefore variable (3). Compared with other preparations in its class, tramadol has more blurred effects of sedation or respiratory depression and the risk of developing tolerance is also lower. However, it decreases the seizure threshold and may trigger serotonin syndrome in subjects treated with tricyclic antidepressants or SSRIs (7, 13, 15).

In patients with hepatic impairment the preferred forms are those with immediate release. Side effects to prolonged release forms are more capricious and more difficult to manage, with high risk of accumulation.
In cirrhosis, the recommended dose is 50mg/per os at 12 hours, with an increase in the interval between administrations. Caution should be exercised in patients with depression and those with a history of seizures should be avoided (13).

1. **STAGE III**

1. MORPHINE
In advanced liver disease and cirrhosis it was found to have low plasma clearance, increased bioavailability and half-life (3).
It has two main metabolites, one with antalgic activity and the other with neurotoxic (confusion, seizures, respiratory depression) effects. The expert opinions are that people with liver pathology should be administered with cautious morphine, double the time between administrations and using a reduced oral dose. If the patient suffers concomitantly from chronic kidney disease, morphine should not be given (risk of seizures, respiratory distress, and hepatic encephalopathy) (4).
The treatment will be initiated with 5 mg once every 6 hours, orally (13, 16).
2. OXYCODONE
Due to poor liver metabolism in advanced stages of hepatic impairment, the analgesic potency is highly variable and influenced (3). Half-life is prolonged and there is risk for high plasma concentrations due to high capacity for binding protein.
Should be administered with caution, at low doses and increasing the interval between them (7, 17). It's highly recommended to avoid prolonged release forms (13). The recommended dose is 5 mg once every 6 hours, orally (13).
3. FENTANYL
It's a synthetic compound of morphine, with superior potency, with strong tropism for proteins, is converted to the liver into inactive and non-toxic compounds (18). It would appear that it could be safely administered to those with minor hepatic impairment, reducing the dosage to those with hypoalbuminemia (4, 13).
Applying transdermal patches can only be considered after an inventory of the daily need for short-acting opioids (13).
4. METADONE
It is considered to be a safe option for people with severe hepatic impairment or cirrhosis for short period of time despite prolonged half-life. It is important to mention that dose reduction is required in case of hypoalbuminemia (4, 13).

ADJUVANT ANALGESICS

1. GABAPENTIN and 2. PREGABALIN
They are included in the class of anticonvulsants. These drugs are not metabolized in the liver and do not bind to plasma proteins, but their elimination is dependent on kidney function (4). However, case studies have been reported with pregabalin-induced hepatic toxicity (19). Posology is the usual one, with progressive titration.
3. DEXAMETHAZONE
In patients with severe hepatic dysfunction, due to increased half-life and hypoalbuminemia an increase in the biological effects has been observed, and numerous side effects are also under discussion (20, 21). Dose reduction is required (22).
4. NORTRIPTILINA
It is preferable to amitriptyline or imipramine due to the diminished sedation effect and the lower probability of accumulation of its metabolites (13). It presents dose-dependent side effects, mostly anticholinergic and cardiovascular (7, 8, 11). Treatment will be initiated with 10 mg orally before bedtime, with the possibility of progressively increasing up to 25 mg (4, 13).

OTHER COMMON USED DRUGS

1. COLCHICINE
In mild-moderate hepatic impairment: no dose adjustment is required, but patients should be carefully monitored to assess possible adverse effects.
In severe hepatic insufficiency: no dose adjustment is required, but a treatment cure should not be repeated more than once every two weeks. For patients requiring repeated treatments, alternative therapy should be considered (23).
2. ALLOPURINOL
Hepatic side effects reported were generally mild. Numbers of patients with transaminases level more than 3 times greater than normal were low. During treatment liver function should be monitored. Several cases of hepatotoxicity have been observed in patients treated with allopurinol, and in some patients asymptomatic elevations of alkaline phosphatase or

serum transaminases have been observed. In patients with pre-existing liver disease, it is recommended to periodically check liver function in the early stages of treatment. In patients with hepatic impairment, it is recommended to reduce allopurinol doses (21, 24).

3. FEBUXOSTAT

In mild or moderate hepatic dysfunction dose adjustments are not needed. The recommended dose is 80 mg orally every second day (24, 25).

Conclusions: Obtaining analgesia in patients with liver disease is a challenge both in terms of the effectiveness of the medication administered and its safety profile. In principle, most pain medication are likely to be useful for this category of patients despite the potential for hepatotoxicity as long as they work with reduced doses and increased intervals between administrations. It is preferable for fast acting drugs and not prolonged release initially with the lowest dose.

Conflicts of interest

The authors of this paper state that there are no conflicts of interest regarding the study methodology, results and conclusions drawn.

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Young patients with myocardial infarction – particularities of cardiovascular rehabilitation

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Abstract

Acute coronary syndromes (ACS) are one of the main causes of morbidity and mortality in the world. It affects people in the middle and late-life, but the biggest psycho-social and financial impact is among the active young population. After the acute event they have to return to work and to their families for which they represent the principal support. Besides medication and prompt revascularization therapies, cardiac rehabilitation (CR) has an important role in regaining most of the initial physical and psychological state. Despite the proved benefit of the CR, referral and participation rate is very low, suggesting that there is more to do in this old but very underappreciated field.

Key words: *acute coronary syndromes, myocardial infarction, young, cardiac rehabilitation, secondary prevention*,

1 Introduction

Cardiovascular diseases (CVD) continue to be the main cause of mortality worldwide and represent almost a quarter of all diseases in Europe, while the costs involved for their treatment are considerable (1). Within 5 years of acute myocardial infarction (MI), about 15% of men and 22% of women aged up to 65 years will have a recurrence (2). Hence the importance of secondary prevention. In addition to the initiated treatment, lifestyle changing and cardiac rehabilitation (CR) are methods that have undeniably proved their efficacy. These consist of long-duration programs involving medical visits, prescription of physical exercise, modification of risk factors, education and counseling (3). Up to 90% of coronary disease cases occur in the context of well-known associated risk factors, among which smoking, sedentary lifestyle and inadequate diet stand out (4). The benefits of CR are well-established, and international guidelines recommend routine CR in standard treatment after MI. Thus, AHA/ACC guidelines for the treatment of patients with acute MI with ST elevation present it as a class I recommendation, while according to ESC guidelines, this is a class IIa recommendation (5,6). Exercise can be considered a preventive method, a "pill" that should be administered daily due to its beneficial effects (7). Young patients who have suffered an acute coronary event represent a special class in that they are most often extremely active persons who are at a delicate time of their life. They have stressful tasks at work, many familial responsibilities, small children and most frequently also parents in their care (8).

2 History

Recommendations related to CR have radically changed over the past decades. Initially, in the 1940's, patients who suffered a MI were advised to completely avoid physical exercise during convalescence, limiting themselves to rest in bed and subsequently in an armchair. In the 1950's, short daily walks for 3-5 minutes were recommended and only in the 1960's the first structured CR protocols were recommended at days after the acute event, through more sustained regular physical exercise (3). In Europe, the first physical exercise recommendations after a cardiac event were those of the German physician Max Oertel in 1885. His principles were applied later, in the 1950's, by Peter Beckman, and the first official CR program was launched in the 1970's in Hamburg, Germany (9). The first CR working group was created in 1982, as part of the European Society of Cardiology, and in 2004, the European Association for Cardiovascular Prevention and Rehabilitation (EACVPR) was founded (9). In the 60's, the first preventive cardiology and rehabilitation centers emerged in Romania, initially in Bucharest, under the leadership of Ioan Orha who also elaborated the first recommendations in the field, and subsequently, in other Romanian cities: Iași, Cluj-Napoca, Târgu Mureș, Timișoara and Covasna (10-12).

3 Evidence

The first clear evidence regarding the efficacy of CR was provided by systematic reviews and meta-analyses published more than 20 years ago. These showed a 20-25% reduction of all-cause and cardiovascular mortality through the analysis of 22 randomized trials with a number of over 4300 patients. In the meantime, several improved versions were published (3). One of them was aimed at evaluating the effects of CR in post-MI patients who attended a standard program for at least 2 weeks, compared to those who did not benefit from such interventions. Thus, 34 randomized clinical studies with more than 6000 patients were selected. A diminution of MI recurrence risk (OR 0.53, 95% CI 0.38-0.76), a reduction of cardiac-cause mortality (OR 0.64, 95% CI 0.46-0.88), as well as overall mortality (OR 0.74, 95% CI 0.58-0.95) were shown (13). Beneficial effects were also obtained on the incidence of cardiovascular RF: smoking, blood pressure (BP), body mass index (BMI), and plasma lipid profile. Besides the fact that even short period of CR was shown to have a positive impact, this persisted beyond the time of active period.

A series of imaging studies have shown an improvement of myocardial perfusion in patients who attended a supervised post-MI program of physical exercise, showing that the positive effect is not related only due to the peripheral physiological adaptation but to the afore development of collateral circulation also. Gunning et al. demonstrated a decrease in the perfusion defect using scintigraphy, as well as a reduction in the severity of the defect in patients enrolled in a 6-week CR protocol, consisting of 20-minute exercise to a target heart rate between 60-80% of age-related maximum (14). Another study conducted by Lee et al. showed that a 3-month CR program carried out at an effort intensity determining a consumption of 55-70% of VO2 max led to an improvement of the myocardial perfusion reserve (MRI-quantified) by 25% in the infarcted area ($p<0.05$) and by 30% in the adjacent myocardium ($p<0.01$), with a consecutive increase in exercise capacity (15). Regarding the patients with left ventricular dysfunction (ultrasound-based), Sadeghi et al. revealed that those who attended a physical rehabilitation program for 8 weeks had a clear improvement in kinetics, with an increase in the left ventricular ejection fraction from 45.14%±5.77% to 50.44%±8.70% ($p<0.001$) (16).

A recently published systematic Cochrane meta-analysis shows the most important evidence of efficacy of physical exercise-based CR in terms of mortality, morbidity and quality of life in patients with ischemic heart disease (17). The meta-analysis comprised 63 studies published until July 2014, found in Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL and Science Citation Index Expanded databases. These included almost 15,000 patients, with more than 80% post-MI patients, the rest being in the coronary revascularization group. The mean follow-up period was 12 months, and most of the studies had small size samples (between 28 and 2304 patients, on average 126 patients/study). A significant reduction in cardiovascular-cause mortality (RR 0.74, 95% CI 0.64-0.86), in the rate of hospitalization (RR 0.82, 95% CI 0.70-0.96) as well as an improved health-related quality of life (HRQL) was observed, especially in younger men, but there were no differences regarding overall mortality (RR 0.96, 95% CI 0.88-1.04), the rate of MI (RR 0.90, 95% CI 0.79-1.07) or the rate of surgical coronary revascularization (RR 0.96, 95% CI 0.80-1.16), and percutaneous coronary revascularization, respectively (RR 0.85, 95% CI 0.70-1.04) (17). The analysis of the 20 studies that assessed quality of life demonstrated beneficial effects of CR in this regard, while other studies showed a favorable cost-effectiveness ratio (18,19).

A Scandinavian trial investigated the impact of a 5-year intensive lifestyle modification which included physical exercise, smoking cessation, dietary advice and stress management in younger women with cardio-vascular disease (CVD) and demonstrated a reduction in the presentation to the emergency department, in work absenteeism and positive effect on quality of life and public finances (20).

Pouche et al. published similar results regarding the impact of CR on mortality. Participants in the 2005 French FAST MI registry were followed up over a 5-year period for the impact of the CR program on survival (21). Although the rate of prescription of CR was low (22%), there was a benefit particularly in the reduction of mortality (by approximately 25%), due to better control of RF, improved functional capacity and better patient compliance with treatment (21). After multivariate analysis, the effect was different in certain subpopulations. Young patients (aged less

than 60 years) had a 66% reduction of mortality. Also, men and patients with MI without ST segment elevation benefited more from CR programs.

The efficacy of CR programs depends on certain standards that must be implemented and respected. Hence the need for programs for monitoring and quantifying the application of CR protocols. The first program of this type in Europe was Carinex Survey in 2002 (22), then ECRIS (European Cardiac Rehabilitation Inventory Survey) in 2008 (23). These provided information about the structure, legislation, financing and implementation of CR programs at national level. However, they did not provide clinical and efficacy data. The latest European project that was materialized was EuroCaReD (European Cardiac Rehabilitation Registry and Database), which was aimed at analyzing current CR practice in Europe based on an electronic data collection system (1). Data provided by 12 European countries, including Romania, regarding patients' basic characteristics, CR indications, treatment and evolution were recorded. The most frequent risk factors: hyperlipidemia, hypertension, sedentary lifestyle and smoking were identified. The most frequent indications of CR were acute coronary syndrome, post-PCI state electively and post-cardiac surgery state, and only 15% of patients did not complete the program. At least half of the patients benefited from CR, with an improvement in exercise capacity by at least 25W. These were mainly young people aged less than 50 years, STEMI and post-surgery patients. Extremely heterogeneous findings were observed regarding the content, duration and place of CR. In Central and Eastern European countries, CR is initiated in hospital, and total duration is shorter, while evidence of efficacy provided by the literature is based on longer duration programs involving more sessions (1).

4.CR. Definition and protocol

The most accurate definition was launched by the British Association for Cardiovascular Prevention and Rehabilitation (BACPR): "The coordinated sum of activities required to influence favorably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behavior, slow or reverse progression of disease" (17).

The current concept of CR comprises that it should be started immediately after the acute event or following the interventional procedure. Once started it should be continuous, staged and individualized depending on the patient preference and tolerance (24).

In the initial ECRIS study conducted by EACPR (European Association for Cardiovascular Prevention and Rehabilitation), CR was structured into three stages (23). The first two take place in the acute phase and are mandatory, preparing the patient for the out-of-hospital activity.

4.1. First stage (early in-hospital rehabilitation)

After the pharmacotherapy initiation and the revascularization procedure, the patient is immobilized for 12-48 hours, depending on the clinical situation. He is informed about the disease, the severity of it and he is counselled for anxiety reduction and mental support. At the same time, psychosocial factors must be identified, which are extremely important in the case of young patients in particular, who are often exposed to stress at their workplace.

The inpatient performs mild exercise in order to recover minimum exercise capacity, required for daily routine activities. At first, this was recommended daily over 1-2 weeks, but with the successful implementation of revascularization procedures, it was minimized, due to immediate recovery of cardiac function (25).

In this situation, the importance of this stage resides in completely safe testing of patient's exercise capacity. Reassuring that the patient is stabilized doing minor in-room activities for itself, exercise of gradually increased intensity is initiated under physiotherapist supervision after 48 hours.

Also, at this stage, both the patient and the patient's family should be informed about the risk factors that have caused acute coronary syndrome and about the importance of cardiovascular prevention medication (statins, converting-enzyme inhibitors/sartans, antiplatelet drugs and beta-blockers).

4.2 Second stage

The proper rehabilitation is initiated 10-20 days after infarction, depending on the initial evolution of the disease, the treatment applied and the patient's exercise tolerance. This is recommended to be initiated in a specialized rehabilitation center, in collaboration with a team of kinesiotherapists, psychologists and dieticians, and can last up to 16 weeks. It consists of carefully monitored physical and

psycho-educational activities (25).

The program starts with the performing of a standardized exercise test that will assess the patient's exercise capacity, residual myocardial ischemia and the presence of rhythm or conduction disorders. Patients with reduced exercise capacity (less than 5 METs) and/or exertional heart failure events will attend a moderate exercise program and will be carefully monitored in a dedicated residential or outpatient center. Patients with good tolerance will perform a physical activity program including at least 36 sessions (between 3 and 5 per week) with the aim of improving exercise capacity by 25-30% or reaching the threshold of 7 METs (25-27). On the other hand, the recent European Register on Cardio rehabilitation Euro Ca Re D defines successful CR as an increase in the exercise capacity by more than 25W, a target reached by only 58% of patients, particularly young and/or active patients (1). Physical exercises, particularly dynamic, on the cycle ergometer, but also static, by light weight lifting, will be performed. The intensity of training can be rigorously estimated initially using the cardiopulmonary exercise test (as metabolic equivalents – METs or percentage of VO2max), but most frequently, it is estimated based on the heart rate reached, which should not exceed 70% and 85% of the maximum heart rate in patients with low tolerance and trained subjects, respectively. This stage ends when the exercise test evidences an exercise capacity of 7 METs; otherwise, it is prolonged precisely in order to reach this threshold (25-27).

4.3 Third stage

This stage should be long-term, ideally lasting throughout the whole life, and is a basic component of patient's lifestyle changing. It consists of maintaining the previously obtained exercise capacity and is carried out individually and without supervision. It corresponds to maintenance physical activity recommended for healthy persons and consists of performing exercises for at least 30 minutes, ideally 60 minutes daily, 5 days a week (25). These may vary depending on the patient's ability and preference: from gardening, brisk walking, static cycling to higher intensity practice of team sports.

A particular form of residential rehabilitation that can be applied in Romania is the one used in the Hospital of Cardiovascular Diseases Covasna, which is unique in Europe due mainly to the special climate conditions (10-12).

Conclusions

Enrollment of young patients with a history of myocardial infarction in cardiovascular rehabilitation programs is beneficial, being accompanied by an increase in exercise capacity, as well as by a reduction in the rate of adverse cardiovascular events, contributing to their rapid socio-professional reintegration. In this context, implementing non-pharmacological and pharmacological secondary prevention measures will also be possible.

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Is segmental muscle strength recovery different patients with dominant versus non-dominant hemispheric ischemic stroke?

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Abstract

Introduction & objectives: Starting from the well-known functional hemispheric asymmetry and concomitantly, from the clinical findings of practitioners involved in the post-stroke rehabilitation process, the aim of this study was to evaluate whether ischemic stroke in the dominant hemisphere results in more severe initial motor deficit and if its motor recovery is decreased compared to that of the non-dominant hemisphere.

Material and method: This was a retrospective study, comprising 39 patients with ischemic stroke in the middle cerebral artery territory, divided into two groups depending on the hemispheric location of the lesion (left/right). They were evaluated for their segmental muscle strength using the Medical Research Council Muscle Strength Grading Scale, both in terms of initial value and evolution between two successive admissions.

Results and conclusions: No significant difference was found for motor deficit evaluated on the occasion of the first admission between patients with left-side stroke and those with right-side stroke. Motor recovery was more obvious proximally in the paretic limbs, but without statistical significance.

Key words: *hemispheric dominance, functional laterality, stroke, motor rehabilitation*,

1 Introduction

Functional laterality correlated with hemispheric dominance is innate and genetically controlled, even if the genes involved are not yet well-known. Functional asymmetry between the two hemispheres is recognized, the left hemisphere being related to reason, logic and language, while the right hemisphere is associated with creativity and visual-spatial perception. Ninety percent of individuals are right-handed (dominant left hemisphere) and the rest of about 10% are left-handed (dominant right hemisphere) (1-3).

Stroke in the middle cerebral artery (sylvian artery) territory will result in contralateral hemiparesis, possibly contralateral hemihypoesthesia and/or hemi/quadrantanopia, but other associated symptoms depend on the hemispheric location of the lesion. Left side location will be associated with aphasia or apraxia, while right side location will associate spatial neglect contralateral to the lesion, anosognosia, visual spatial perceptual disorder, body image deficit, postural malalignment. This explains the hypothesis that a left-side sylvian ischemic stroke will lead to more severe motor deficit, the left hemisphere playing a more important role in the control of motor behavior compared to the right hemisphere (4-6). On the other hand the right side stroke seems to be more common and also associated with significantly higher morbidity (7). Can the stroke hemispheric localization be considered as a biomarker beside the neuroimaging, electrophysiological or biochemical biomarkers? Moreover, can it contribute to the motor outcome prediction? (8-10)

Material and method

A retrospective study was conducted, which included 39 patients with ischemic stroke in the sylvian territory (middle cerebral artery - MCA) with contralateral hemiparesis, admitted to the services of Neurology I and Neurology II of the Rehabilitation Hospital Cluj-Napoca, in the period 01.01.2017-30.06.2018 (1.5 years). The inclusion criteria were age over 18 years, stroke occurring within the last 2

years, its confirmation by neuroimaging, and 2 consecutive admissions for motor rehabilitation in the mentioned time period. From the observation sheets, demographic data, the hemispheric location of the cerebral infarction and the Medical Research Council Muscle Strength Grading Scale (MRC S) values for paretic limbs (proximal and distal) were collected; for each admission, 4 values of MRC S were obtained which corresponded to upper limb-proximal (ULP), upper limb-distal (ULD), lower limb-proximal (LLP) and lower limb-distal (LLD). The patients were assigned to two groups according to the hemispheric location (right/left) of the stroke. Due to the retrospective lack of data related to the hemispheric dominance of the patients, it was considered that the left hemisphere was dominant and the right hemisphere was non-dominant in the studied patients (based on the literature statistical data, 90% of individuals being right-handed).

The Medical Research Council Muscle Strength Grading Scale (MRC S) is an assessment tool for segmental motor deficit including 5 grades: 0 – no movement; 1 – flicker or trace contraction; 2 – active movement with gravity eliminated; 3 – active movements against gravity but not against resistance; 4 – active movements against resistance; 5 – normal power (11).

Statistical analysis was performed using Microsoft Excel. Categorical data were presented as diagrams, absolute and relative frequencies, and continuous variables were summarized using synthetic centrality, dispersion and location indicators or frequency histograms. Statistical analysis used the paired and unpaired t test. A p value lower than 0.05 allows rejection of the null hypothesis (H0) and acceptance of the alternative hypothesis (H1).

Results

Of the 39 patients, 36% were women and 64% were men, distributed by age groups as shown in Figure 1. Regarding the two groups of patients, with left MCA stroke and right MCA stroke, they were relatively equal both in terms of number of patients in each group and sex distribution (Table 1, Fig 1).

Table 1: Distribution of the two hemispheric locations depending on gender

Sex	Left MCA stroke	Right MCA stroke
Women	7	7
Men	12	13
Total	19	20

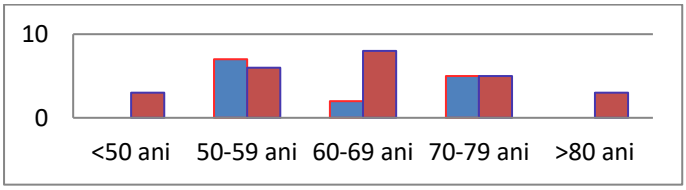

Fig. 1. Distribution of cases by age and sex (blue – women, red – men)

By comparing the mean MRC scale (MRC S) values for the paretic limbs (ULP, ULD, LLP, LLD) using the paired **t** test, statistically significant increases (improvements) were found for both paretic limbs, both proximally and distally ($p<0.05$), especially for the proximal upper limb (Fig.2).

By comparing the initial mean MRC S values between patients with left MCA stroke and right MCA stroke (reflecting the initial motor deficit at the patients' presentation to the Rehabilitation Hospital), no statistically significant results were obtained; so, the null hypothesis that the motor deficit assessed by MRC S is similar in the case of left-side stroke (dominant hemisphere) and right-side stroke (non-dominant hemisphere) is not rejected, but we can observe a lower mean value of MCR for the proximal region of the paretic upper limb (Fig. 3).

The two groups (right MCA stroke and left MCA stroke) were also compared for the difference of the mean values by which MRC S improved between the two admissions (Fig. 4) using the **t** unpaired test (Fig. 4)**.** It can be seen that the improvement in MRC S values for the proximal region of both the upper limb and the lower limb is more obvious in the case of the right side location of stroke, while for the distal region of the upper limb the improvement is more marked for the right side location of stroke and is about the same for the distal region of the lower limb. However, p values >0.05 do not allow to reject the null hypothesis that there is no significant difference in the evolution of motor deficit in paretic limbs between the left and right side location of ischemic stroke.

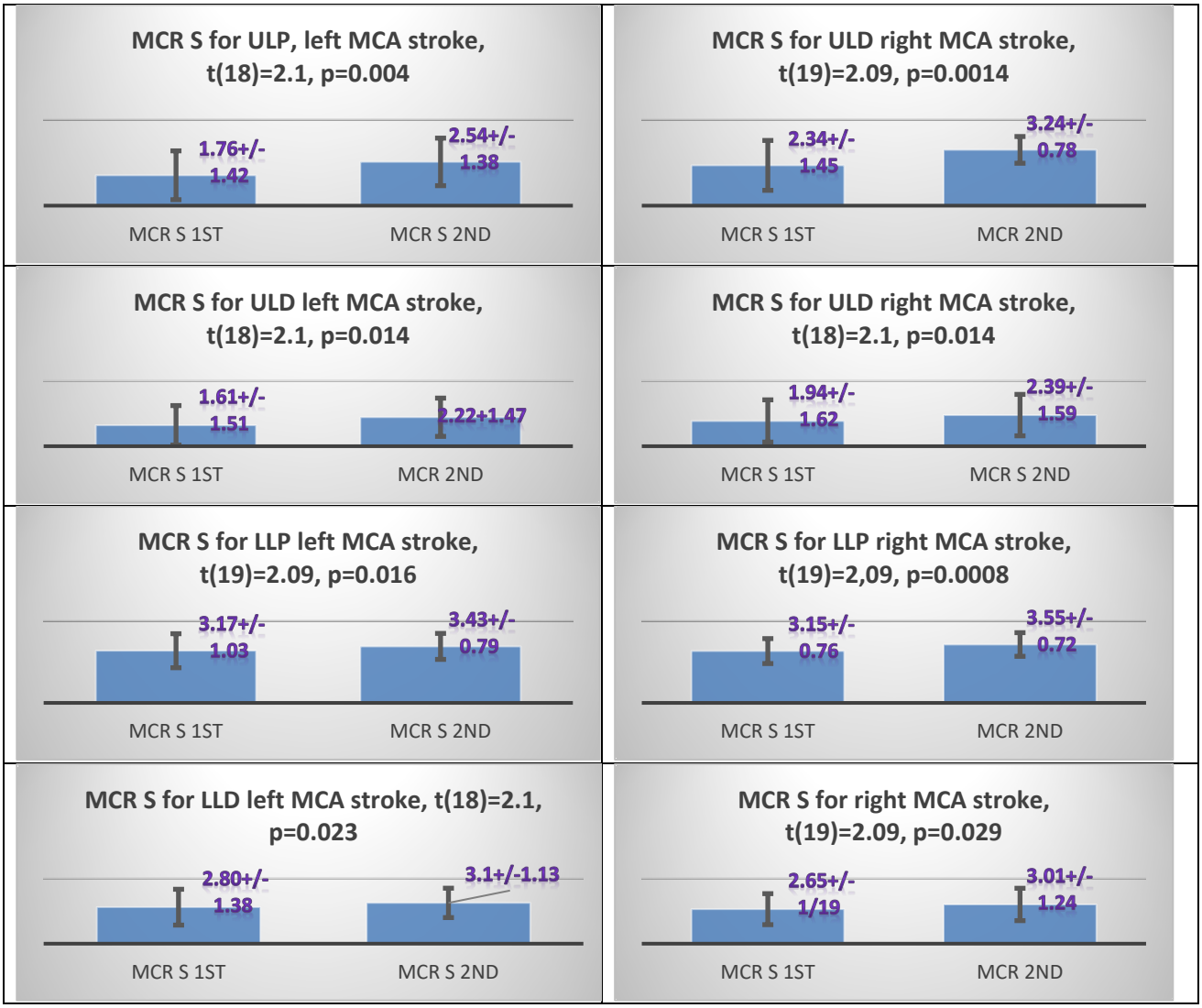

Fig.2. The improvement of MCR S for each paretic limb (proximal and distal) for left and right MCA stroke, according to paired **t** test analysis.

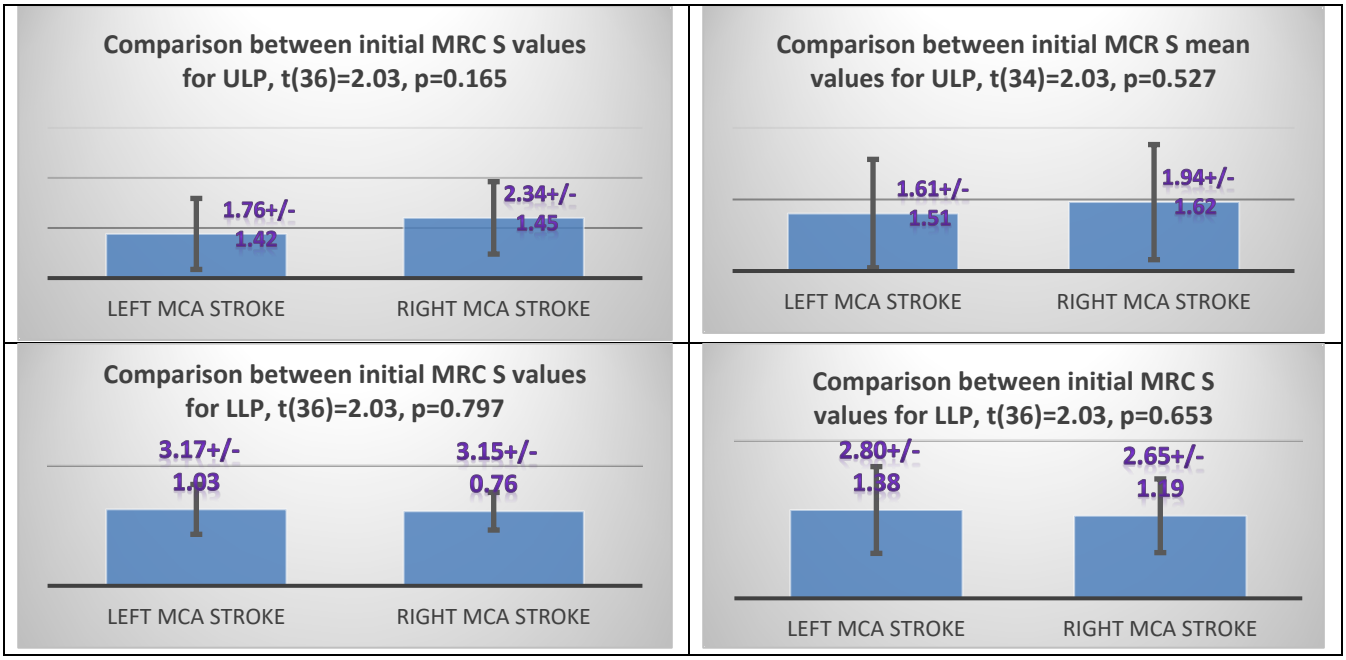

Fig. 3. Initial mean values for MRC S (left vs right MCA stroke) according to unpaired **t** test analysis (first admission)

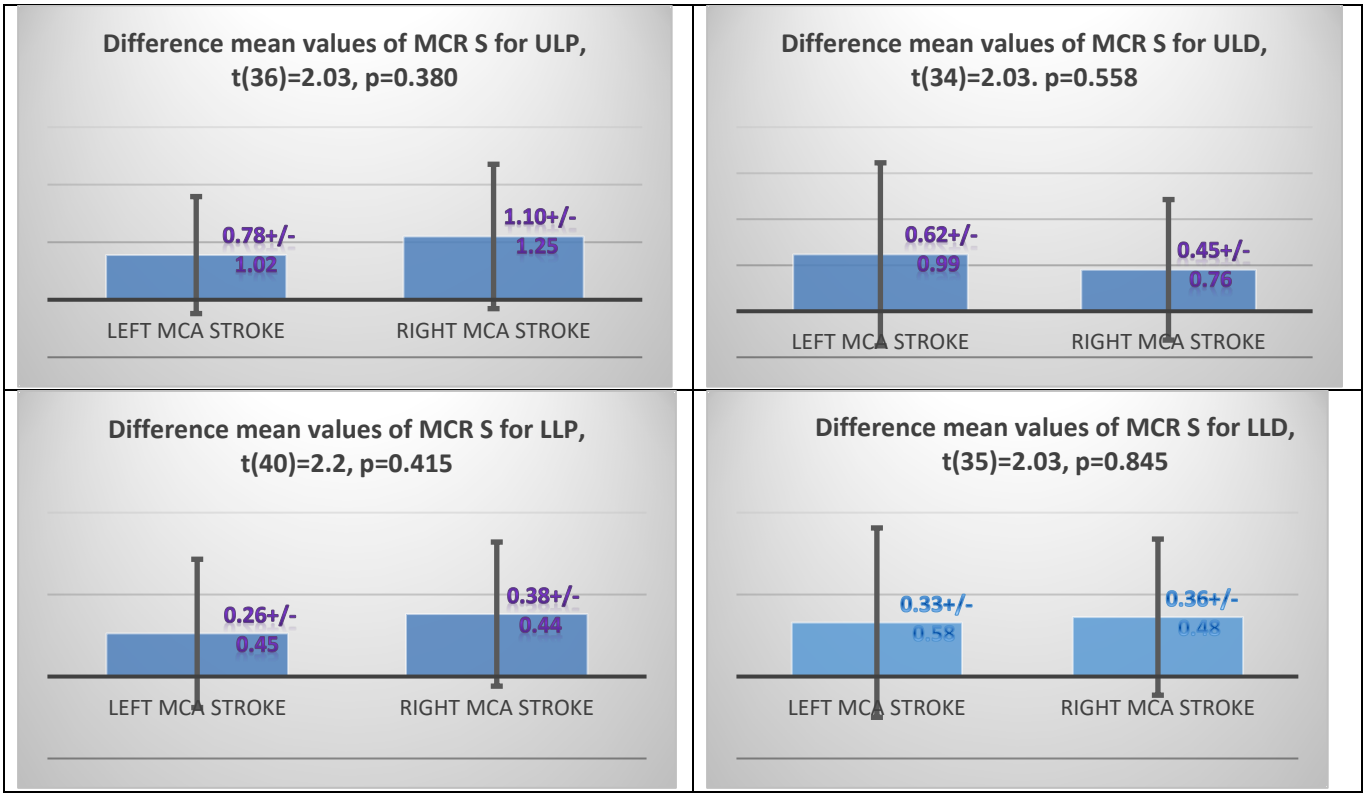

Fig.4. Difference MRC S mean values for each limb (proximal and distal), left vs right MCA stroke, between the two admissions, according to unpaired **t** test analysis

Conclusion

In healthy persons, the dominant upper limb (the right limb for the majority) is superior to the non-dominant one in tasks that demand precision, speed, coordination and muscle strength. Consequently, clinical practitioners (neurologists, kinesiotherapists, occupational therapists) frequently believe that motor deficit is more pronounced in the case of left-side stroke and functional rehabilitation of patients with left-side stroke is worse than that of patients with right-side stroke, supposing that impairments of the dominant (right) upper limb would be more detrimental for activities of daily living compared to impairments of the non-dominant side (left), supported by some reports (4, 5) and not by others (12, 13). Our research could not validate this hypothesis for the grade of motor deficit (measured by the MRC Muscle Strength Grading Scale at the first admission).

Also, for the degree of motor deficit recovery (reflected by the difference in MRC Muscle Strength Grading Scale between the second and the first admission), the results were not statistically significant, but a greater improvement in proximal muscle strength in the paretic limbs was observed in our study for the right side location. Due to the retrospective nature of the study, only the data available in the observation sheets were used, while information about the assessment of the evolution of other aspects of motor rehabilitation such as coordination, posture and walking was absent. Associating this aspects some authors concluded that left MCA strokes have a worse outcome than their right-hemispheric counterparts (4, 5). More extensive studies are probably required, which can provide additional information based on a differentiated approach to patients with dominant versus non-dominant hemispheric stroke.

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Functional outcome after symtomatic internal carotid artery occlusion

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Abstract

Internal carotid artery occlusion accounts for 15-20% of ischemic strokes, caused by atherosclerosis or dissection. Clinical symptoms are variable, from asymptomatic cases to minor or severe strokes. Diagnosis in internal carotid artery (ICA) occlusion is based on imaging techniques. Prognosis after ICA occlusion depends on many factors: severity of neurologic deficit, spontaneous recanalization of the artery, and the occurrence of recurrent strokes. Patients with spontaneous recanalization of the occluded ICA tend to have a retained functional ability and favorable clinical outcomes. Medical treatment, recanalization techniques and intensive rehabilitation program are essential in improving functional outcome of patients with stroke produced by ICA occlusion. We present the case of a young patient diagnosed with ischemic stroke produced by internal carotid artery occlusion, with consecutive severe neurologic deficit, and an unfavorable functional outcome, as evaluated with the Modified Rankin Scale. Spontaneous recanalization of the occluded ICA was observed after 6 weeks, suggesting a carotid dissection. The patient was included in an intensive rehabilitation program, associated with best medical therapy, showing improvement of its functional status at 3 months follow up.

Key words: *ischemic stroke, carotid artery occlusion, carotid dissection, spontaneous recanalization, functional outcome*,

1 Introduction

Internal carotid artery (ICA) occlusion is a frequent cause of ischemic stroke. In general population, the real prevalence and incidence of ICA occlusion is difficult to assess, because many patients remain asymptomatic or are not investigated (1).

ICA occlusion is produced by atherosclerotic disease, cardioembolism, dissection or radio-therapy (2, 3). Clinical symptoms are variable, from asymptomatic cases to minor or severe strokes. Diagnosis in symptomatic ICA occlusion is based on one of the following imaging techniques, used concurrently: Doppler ultrasound examination of cervical arteries, computer tomograph angiography (CTA), magnetic resonance angiography (MRA) and digital substraction arteriography (DSA) (2).

Asymptomatic patients with ICA occlusion have a favourable outcome, but symptomatic ICA occlusions are associated with important disabilities and carried also an important risk of recurrent strokes. Spontaneous recanalization of the occluded ICA is not a rare event, it has been described in up to 10% of the patients, especially in ICA dissection with secondary occlusion, and in the first weeks after stroke (3, 4, 5). Patients with late spontaneous recanalization of the occluded ICA tend to have a retained functional ability and favorable clinical outcomes (6).

Treatment options in ischemic strokes caused by ICA occlusion are not different of standard ischemic stroke treatment in the acute phase. In chronic phase, best medical treatment combined with surgical or endovascular recanalization techniques could help in obtaining a functional improvement.

Case report:

A 45 years old male patient, smoker, with moderate alcohol consumption, was admitted in the Emergency Department for severe left hemiplegia. Mild right hemicrania was then reported. Emergency native CT scan showed acute infarctus in the right middle cerebral artery (MCA) territory (images not shown). Intravenous thrombolysis was not performed, due to unknown onset time. Doppler ultrasound of cervical arteries showed complete occlusion of the right ICA. Blood pressure values were normal. Cardiologic assessment (including transthoracic echocardiography and 24 hours Holter-ECG) was unremarkable.

Blood tests revealed slightly elevated cholesterol and triglyceride levels. The patient was discharged on antiplatelet (clopidogrel) and statin treatment.

Six weeks after the acute stroke, he was admitted in our Rehabilitation hospital. He reported intermittent headache exacerbation. Neurological assessment showed severe left hemiparesis with brachial predominance (muscle force quotation of 1/5 in left upper limb and 3/5 in left lower limb), left hypoesthesia, and severely impaired gait requiring bilateral assistance. Functional assessment showed a modified Rankin Scale (mRS) of 4, the patient being completely dependent in his daily activities. Native CT scan showed large chronic ischemic area in the right MCA territory **(Figure 1).**

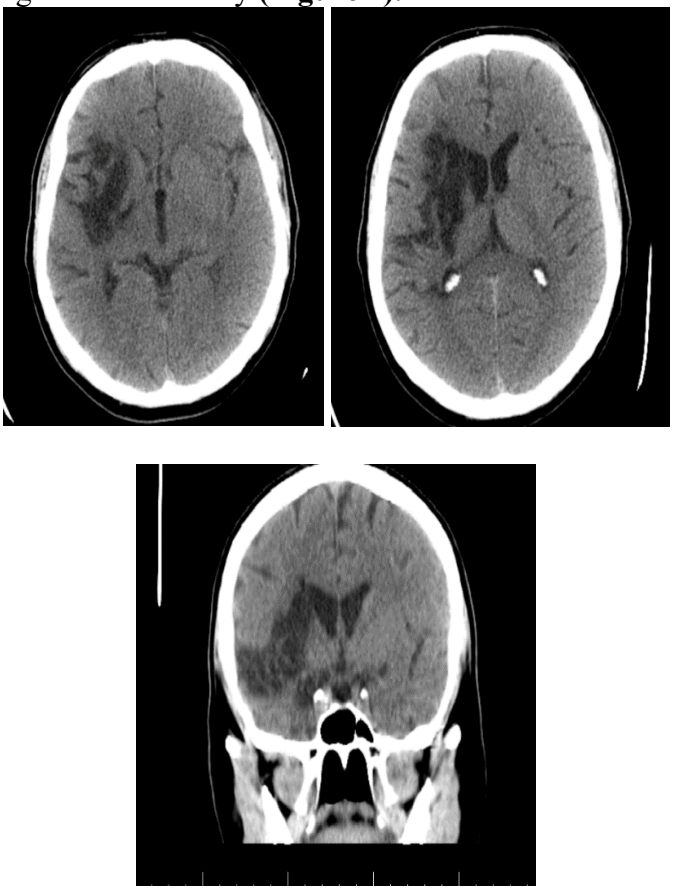

Fig. 1: Native CT scan 6 weeks after stroke onset showing chronic ischemic area in the territory of the right MCA

Doppler ultrasound of cervical arteries was repeated, and showed eccentric flow in the right ICA. CTA was then performed, and confirmed recanalization of the right ICA **(Figures 2 and 3).**

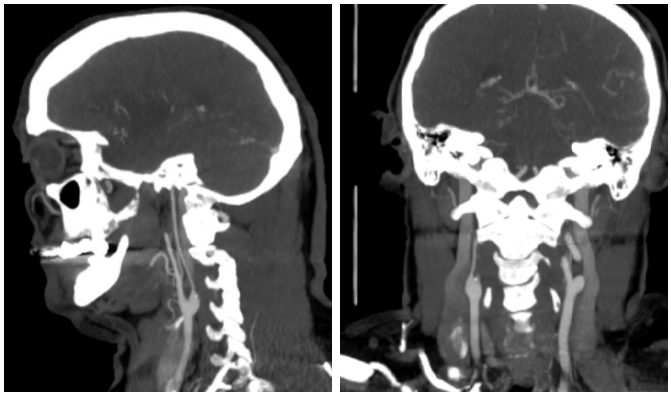

Fig. 2: Recanalization of the extracranial right ICA from origin to intracranial segments, suggestive for dissection (right- lateral view, left – coronal view)

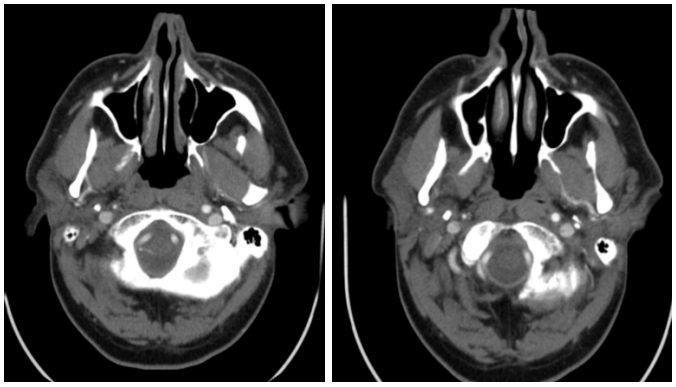

Fig. 3: Recanalization of intracranial segment of right ICA

The length of previous stenosis, with early recanalization, which extends intracranially, suggest an ICA dissection as the cause of ICA occlusion. Conservative medical treatment was chosen for our patient, carotid artery dissections have generally a good prognosis. The patient was discharged on antiplatelet (clopidogrel) and statin treatment. Control Doppler ultrasound was settled after 3 months.

The patient was admitted in an intensive rehabilitation program. The physical therapy methods consisted in sedative massage of the dorsal and lumbar paravertebral muscles, postural exercises and passive mobilization of the paralyzed limbs to prevent tendinous retractions and respiratory exercises. For upper limb function, task-specific motor training, oriented towards achieving daily activity goals, and virtual therapy were used. Gait training included assisted walking on the parallel bar system. Robotic devices were used for improvement of upper and lower limb functions.

For lower limbs, intelligent control of walking was provided by a robotic system, which allowed partial support of patient's body weight with walking assistance depending of patient's muscle force and movement capacity. For upper limb, a prototype of exoskeleton device focused of elbow movement was used (7). The rehabilitation program was conducted over three weeks, with mild improvement of motor function.

At 3 months follow-up, patient neurological status improved: muscle force was 3/5 proximally in left upper limb, and 4/5 in right lower limb, the gait was possible with unilateral assistance, and patient regained partial autonomy, with functional improvement and a modified Rankin score of 3 points (8). Doppler ultrasound of cervical arteries confirmed ICA recanalization with high velocity flow.

Results and discussions

Stenosis of extracranial arteries accounts for 15-20% of all ischemic strokes in populational studies (9,10, 11), while extracranial ICA occlusion is responsible for 3,5% (12) reported incidence of ICA occlusion being 6/100 000 individuals (11).

Factors involved in ICA occlusion are atherosclerotic disease, dissection of the extracranial carotid artery, cardioembolism and neck radiotherapy (2, 3). In older persons, ICA occlusion could result from a progression of a tight carotid stenosis (13). Dissection with secondary ICA occlusion is more common in young, and accounts for 2,5% of ischemic strokes (14). Elevated homocysteine levels were also associated with ICA occlusion (15).

In our 45 years old male patient, without main atherosclerosis risk factors, the presumed etiology for ICA occlusion was arterial dissection. Diagnosis of ICA occlusion in our stroke patient relayed on Doppler ultrasound of cervical arteries, CTA and cervical MRA sequences for dissection diagnosis were not performed.

The clinical presentation after an acute ICA occlusion is variable: some persons remain asymptomatic, others have transient ischemic attacks (TIA) or minor strokes, and others have severe strokes (2). The severity of neurologic deficit depends on the presence of collateral circulation and on early recanalization of the artery (16). A study published in 1986 found severe neurologic deficits in all patients with ICA occlusion (17). In our patient, the severity of neurologic deficit could be explained by brutal onset, lack of collateral circulation or a dysfunctional Willis polygon.

Asymptomatic ICA occlusion has a usually a benign evolution, when the collateral cerebral circulation is well-developed and the occluded ICA remains stable ("safe artery") (18). The natural history of symptomatic ICA occlusion carries a risk of recurrent stroke of 5-6% per year (2). A new stroke after a complete ICA occlusion is explained by "carotid stump syndrome" (microemboli from the stump or from ipsilateral external carotid artery occluding middle cerebral artery branches) or by hypoperfusion infarcts in watershed territories (in case of insufficient compensation by collateral circulation) (2). This is the reason why symptomatic ICA occlusion patients required best medical or/and surgical treatments.

Our patient was treated with antiplatelet agents and high-dose statins; no recurrence of ischemia and spontaneous recanalization were observed after 6 months form stroke onset. Diagnosis of spontaneous recanalization was established with Doppler ultrasound, and confirmed with CTA, where the recanalized ICA showed small, irregular diameter which extends from the origin until the beginning of the petrous segment, the shape and length being suggestive of dissection.

Spontaneous recanalization of occluded ICA has variable rates: between 2,3% and 10,3% (4), and is most likely to occur in the acute phase (in the first 2 weeks after occlusion) (19), but was also described in chronic ICA occlusion, after more than 3 months from onset, being considered a rare event (20). Spontaneous recanalization increases the cerebral blood flow in the affected brain area and the risk of subsequent embolic stroke. In occlusions produced by ICA dissection, spontaneous recanalization is more frequent, in 57 to 62% of cases (5), appeared earlier, between 2 days and 6 weeks after stroke, and increased over time (3). The recanalization of an occluded atherosclerotic ICA seems to be a rare event. Mechanisms of late spontaneous recanalization are partially unknown: fibrinolysis and collateral circulation through vasa vasorum (6).

Treatment of ischemic stroke produced by ICA occlusion is not different from treatment of any ischemic stroke, but the prognosis after intravenous thrombolysis treatment seems to be unfavorable at 3 months (21).

The natural history of strokes induced by ICA occlusion showed good recovery in only 2-12% of

patients and important disability in 40-69% of patients (17, 22), as measured by modified Rankin Scale (mRS) (8). Unfavorable outcome with 75% rate of death and disability after 1,2 years of follow up have also been reported in ICA occlusion strokes (23).

In our patient, despite severe hemiplegia induced by stroke, evolution was favorable, with improvement of motor deficit and disability, possibly related to spontaneous recanalization of the occluded right ICA and to intensive rehabilitation program.

Treatment options for chronic extracranial ICA occlusion include best medical treatment (with oral antiplatelet drugs: aspirin or combination of aspirin with clopidorel) – aiming to prevent further strokes, and recanalization therapy: carotid endarterectomy (CEA), stenting (CAS), or hybrid surgery (CEA of the proximal part of ICA and stenting of the distal part) (2). Indications for surgical treatment are still under debate: symptomatic patients, with severe cerebral hemodynamic failure (as measured by PET as increased oxygen extraction extraction fraction OEF) and retrograde filling of ICA are good candidates for surgical recanalization. Recanalization has a succes rate of only 34% (24, 25). For our patient, treatment options included only best medical treatment and rehabilitation. No recurrent strokes were noted on follow up, and patient's functional outcome tends to improve.

Conclusions

Occlusion of internal carotid artery accounts for up to 20% of ischemic strokes. In young people, carotid dissections leading to ICA occlusion are a frequent cause of stroke. Diagnosis relays on concurrent imaging methods. Clinical picture of these particular strokes depends on patient's cerebral hemodynamic particularities and on the possibility of spontaneous recanalization of the occluded artery.

Despite severity of neurological status, spontaneous recanalization could help in improving disability in combination with intensive rehabilitation program, while medical treatment is essential in preventing stroke recurrences.

Endovascular or surgical recanalization of occluded artery is recommended if previous methods have failed in improving functional outcome of patients.

Conflict of interest

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 this study.

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Collaborative platform development in nutrition as support for cardiovascular patients' rehabilitation

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Abstract

Introduction. Enrollment of patients with cardiovascular disease in rehabilitation programs may contribute to implementation of a healthy lifestyle, including by promotion of a diet adequate for each patient's profile. In this context, the current study is aimed at creating a traffic light system model allowing to obtain the development, innovation and diversification of menus and to improve the nutritional programs for this category of patients. **Material and method.** Based on the data provided by USDA Food Composition Databases, the composition in terms of different nutritive principles was determined for each ingredient and for each final menu. Comparison of menus depending on each nutritive principle, as well as comparison between menus and nutrient requirements according to indications for patients attending cardiovascular rehabilitation programs was made. **Results.** The traffic light system was developed, using color codes, comparing daily nutrient requirements with preparations' content. **Conclusions.** The major benefit of the traffic light system would reside in the fact that starting from classic menus, an intervention on these can be achieved, and healthier, more nutritionally balanced models can be created, according to healthy nutrition principles. These new menus will be calorically and nutritionally adapted for patients attending cardiovascular rehabilitation programs.

Key words: *nutrition, rehabilitation, traffic light system*,

1 Introduction

Cardiovascular diseases (heart failure, ischemic disease, stroke) have an increasing prevalence (approximately 48% in adults aged over 20 years), in both sexes (1). They represent the first cause of death worldwide (1, 2), involving increasingly higher treatment and rehabilitation costs (1, 3). Without any doubt, an important role in the occurrence and complications of cardiovascular diseases is played by cardiovascular risk factors. Along with smoking, obesity, diabetes mellitus, dyslipidemia, hypertension, sedentary lifestyle, unhealthy diet is one of the most important modifiable risk factors. Certainly, at present, particular emphasis is also being placed on the evaluation of new cardiovascular risk factors (4, 5) and their implication in the progression of cardiovascular diseases (6). The European Guidelines for the Prevention of Cardiovascular Diseases recommend a healthy diet for all individuals, regardless of the presence or not of cardiovascular diseases (7).

According to the report of the American Heart Association in 2019 (1), about 80% of all cardiovascular diseases can be prevented through a healthy lifestyle, including a healthy diet. The data reported by the European Heart Network show that in Europe nutrition plays a primordial role regarding morbidity and mortality of cardiovascular cause (7). This is why, under conditions of an established cardiac disease, the enrollment of patients in cardiovascular rehabilitation programs may contribute to implementation of a healthy lifestyle, including by promotion of a healthy diet adequate for each patient's profile. In this context, the current study is aimed at creating a traffic light system model

allowing to obtain the development, innovation and diversification of menus and to improve the nutritional programs in patients undergoing cardiovascular rehabilitation.

Methodology of the research – Practical development of the traffic light system

The co-authors have strong expertise not only in their specific fields, but also in applying IT&C related knowledge and skills to various medicine areas, as shown by the following works (8-13).

This time we designed a small collaborative environment to support the traffic light related research by using basic ITC tools adapted to non-technical, but comfortable user experience and pre-existing data structure and layout given by Nutritional DB.

In terms of Design Science research (14), our design problem can be formulated as follows:

- We aim to improve collaboration, data processing and analyze support effectiveness...

1. ...by developing a comfortable ITC-based platform...
2. ...that allows the medical staff to design a traffic light system...
3. ...in order to maximize utility for people to make better and informed nutritional choices.

According to the conceptual design depicted in ERD, its relational mapping was first projected in individual sheets via Google Sheets to ensure data sharing and collaborative work among team members spread in different locations.

Preliminary results

STAGE I – based on the data provided by USDA Food Composition Databases https://ndb.nal.usda.gov/ndb/search/list, the composition in terms of different nutritive principles was determined for each ingredient:

1. Saturated and polyunsaturated fatty acids 04:00, 06:00, 08:00, 10:00,12:00, 14:00, 16:00, 18:00, 20:00, 22;00, 24:00;

- Proteins – including 20 amino acids – leucine, lysine, methionine, valine, arginine, histidine;

Carbohydrates – different types, e.g. fiber, fructose, lactose, maltose, sucrose, galactose;

Vitamins – group B vitamins, folates, vitamins A, C, E, D, K, riboflavin; flavonoids;

Minerals – calcium, magnesium, iron, selenium, zinc, copper;

Energy and total amount of lipids, proteins and carbohydrates.

The centralization of these data for each ingredient led to the creation of a database.

STAGE II – determination of composition in terms of different nutritive principles of the final preparations (soups/basic preparations/garnishes) – based on connections established between recipes – ingredients used – amounts – nutritive principles.

STAGE III – comparison of preparations depending on each nutritive principle, as well as comparison between menus and nutrient requirements according to indications for patients attending cardiovascular rehabilitation programs.

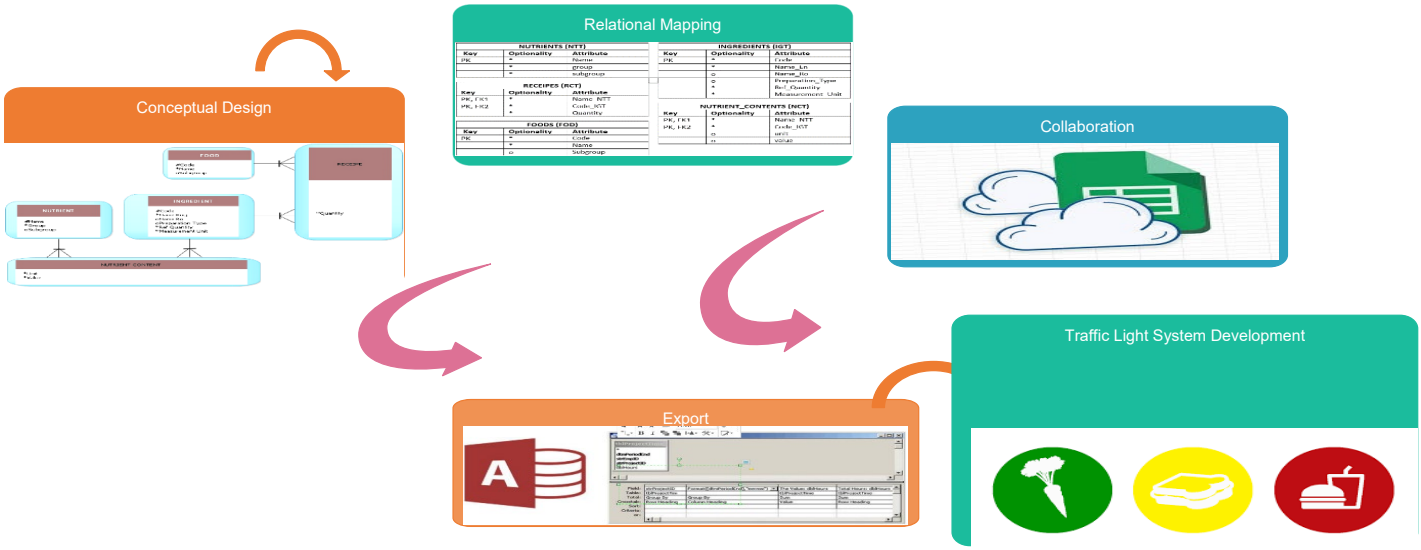
Color codes were used to develop the traffic light system: green – if all daily nutrient requirements were met, yellow – if the studied preparation met more than 60% of the daily nutrient requirements, attention being drawn to the fact that the rest of the daily requirements had to be met by the other preparations consumed, and red – if the amount provided by the studied preparation was less than 60% of the daily requirements. In the case of "unhealthy" nutritive principles (e.g. salt), the system of values was reversed – the preparation being assigned the red color if the value exceeded the limit admitted for the studied age category.

The stages of the development of the traffic light system are presented in Figure 1, and the practical exemplification of the result (for several preparations) is shown in Figure 2.

Discussions

The application of IT&C tools in other areas than the field of computers and particularly in medicine is considered to be promising; modern methods can facilitate both the discovery of new knowledge and the increase in the practical applicability of existing knowledge. They can be included in cardiovascular rehabilitation programs, which during stages I and II are conducted in an organized setting – in hospital or on an outpatient basis (15). The team involved in this program is complex, including, in addition to a cardiologist, nurses, a psychologist/psychiatrist and a kinesiotherapist, a nutritionist.

Fig. 1.– Traffic light system development process flow



Denumire	Riboflavin	Selenium	Sodium	Thiamin	Vitamin A	Vitamin B12	Vitamin C	Vitamin D	Vitamin E	Vitamin K	Zinc
supa crema de linte	2.62	163.29	6350.38	5.23	6045.51	0.00	3.76	0.00	6.24	84.12	10.40
supa crema de mazare	2.77	164.90	6545.21	5.64	8372.22	0.01	43.56	0.00	6.30	134.76	11.24
supa crema de praz si cartofi	2.68	163.95	6378.72	5.24	1609.62	0.06	18.09	17.60	6.72	122.10	9.96
supa crema de rosii cu busuioc	2.66	171.54	7171.03	5.30	8226.19	0.00	68.40	0.00	9.62	127.14	10.32
supa de fasole 400 ml	0.05	0.22	2350.81	0.01	208609.50	0.00	7.94	0.00	2.12	5.27	0.15
supa de pui cu fidea	0.24	28.50	1771.37	0.16	33966.76	0.18	307.95	2.00	3.52	60.80	2.5

Fig. 2. – Traffic light system results – exemplification

Exemplification for: lentil cream soup, green peas cream soup, leek and potato cream soup, tomato and basil cream soup, bean soup, and chicken and noodle soup

After the data population process, the cloud stored file was exported locally, cleaned up, mapped to a database structure, and then analyzed with MS Access tools such as cross-tabs and other various query types. The short time period during which the patient with myocardial infarction treated interventional is hospitalized is extremely important for understanding the cardiovascular risk factors that have led to the development of the disease and for implementing lifestyle changing measures, including those concerning a healthy diet. Next, although rehabilitation is carried out in an outpatient setting (and currently, more and more often at home), the patient should be monitored and evaluated periodically from this point of view as well (16-18). In this regard, creating a "nutritional model" that can be applied to these categories of patients can be of real help.

There are few published studies on the possible uses of various informatics methods in nutrition and particularly among patients enrolled in cardiovascular rehabilitation programs. The great majority of current applications refer to the calculation of the content of lipids + proteins + carbohydrates, provide simple nutritional evaluation methods, without refined analyses and without taking into consideration the particularities and nutritional requirements of the person concerned.

Different types of diets have been studied and assessed regarding their role in the secondary prevention process (19) – Mediterranean diet – in the PREDIMED study - Prevencion con Dieta MEDiterranea (20, 21, 22), Hellenic Heart failure study (23), DASH diet, vegetarian or vegan diets. Controversies related to vegetarian/vegan diets are multiple. The risks of these diets would be nutrient deficiencies (24), lower levels of eicosapentaenoic and docosahexaenoic acids (25-27) – acids involved in cardiovascular disease prevention (24, 28), lower iron stores (24), lower daily intake and serum concentrations of zinc, iodine and vitamin B12 deficiency, decreased vitamin D levels (24,25) with a reduction in bone density, development of osteoporosis, spinal fractures and compression (25). However, a vegetarian diet induces an improvement in the lipid profile, blood pressure values, glycemic

control, a decrease in abdominal obesity (25, 28-33), reduces salt consumption, is rich in potassium, is associated with an increase in the level of physical activity performed (34) and with fewer fatal/non-fatal events in patients with ischemic heart disease (24, 25, 35, 36).

The adaptation of diet to the existing cardiovascular pathology, to the desiderata imposed by the performing of the cardiovascular rehabilitation program (type of physical exercise) and to the subjects' personal characteristics (sex, current weight status, and food preferences) is an extremely sensitive and difficult to achieve process. Current prevention guidelines recommendations are a percentage of trans-unsaturated fatty acids <1% of energy intake, consumption of < 5 g salt/day, limitation of alcoholic drinks and discouragement of sweetened/carbonated drinks (7).

Even if there are studies (pro and con) on the impact that certain nutrients and vitamins may have on cardiovascular pathology (selenium – (37-40), thiamine – (41,42), vitamin C - (43, 44), magnesium – (4-47), zinc (48), monitoring of intake within rehabilitation programs is rarely performed.

The study of food menus and their adaptation to patients' particularities would involve nutritional analysis from the perspective of the recipe and preparation technology, providing information related to the nutritional and energy value of the menus, salt content, fat, saturated fat, sugar and particularly nutrients, vitamins (much more rarely evaluated, as mentioned before). The analysis of menus would identify deficiencies, as well as the possibilities of improvement. At the same time, with the help of specialists in nutrition, menus might be created in accordance with the dietary beliefs of different categories of patients, to reduce nutritional deficiencies and allow effective cardiovascular rehabilitation. Despite seeming an easy process, refined analysis, with the evaluation of micronutrient and vitamin content, is very time-consuming and difficult to perform.

Implementing the traffic light system would allow the development, innovation and diversification of food menus, which would lead to reformulated, personalized menus with practical applicability (by applying knowledge of molecular gastronomy, molecular, nutrigenomic, nutriepigenetic nutrition) for patients attending cardiovascular rehabilitation programs (49-51).

Conclusions

The major benefit of the traffic light system would reside in the fact that starting from classic menus, an intervention on these can be achieved, and healthier, more nutritionally balanced models can be created, according to healthy nutrition principles. These new menus will be calorically and nutritionally adapted for patients attending cardiovascular rehabilitation programs.

Through the collaboration of the cardiologist and the nutritionist, using modern informatics methods, patients will be able to diversify their diet, while respecting the principles of healthy nutrition.

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Left ventricular diastolic dysfunction in diabetes mellitus and the therapeutic role of exercise training

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Abstract

Left ventricular diastolic dysfunction (LVDD) with normal ejection fraction is considered common among people with diabetes mellitus (DM). LVDD is a progressive condition and an independent predictor of mortality in diabetic patients. The etiopathogenesis of LVDD is multifactorial, including diabetes associated comorbidities, such as hypertension, coronary atherosclerosis and obesity, as well as myocardial vascular and metabolic disturbances which lead to diabetic cardiomyopathy. Early stages of LVDD may be detected using echocardiographic techniques. Treatment strategies evolve, based on a better understanding of pathogenic mechanisms, although it is still difficult to efficiently control LVDD evolution. This review synthesizes the main pathophysiological processes and clinical features that characterize DM associated LVDD. Among treatment options, the therapeutic relevance of exercise training programs is underlined.

Key words: *diabetes mellitus, left ventricular diastolic dysfunction, physical training*,

Introduction

Left ventricular diastolic dysfunction (LVDD) is caused by alterations of ventricular diastolic properties with consequences on ventricular stroke volume. It has been shown that nearly half of patients with signs of congestive heart failure have normal ventricular systolic function (1,2), their symptoms being correlated with impaired diastolic function (3,4). It is considered that more than 30% of patients with LVDD and preserved ejection fraction progress to congestive heart failure (5). Community based echocardiographic studies have shown that LVDD has an independent predictive value for all-cause mortality (6).

In diabetic patients, cardiovascular diseases are two to four times more frequent than in the non-diabetic population (7) and are responsible for 80% of diabetic patients' deaths (8). The causes of the association between diabetes mellitus (DM) and cardiovascular diseases are multiple and still incompletely clarified, but coronary atherosclerosis, arterial hypertension (HT) and diabetic cardiomyopathy are important contributors (9).

It has been shown that LVDD with normal ejection fraction is common among people with DM. Its prevalence varies widely (between 47% and 75%) (10,11), possibly because of the different methods used to define and measure LVDD and due to the clinical particularities of the investigated patients. It is largely accepted that LVDD may be the first marker of the preclinical form of diabetic cardiomyopathy. Moreover, it has been shown that LVDD in diabetic patients is predictive of all-cause mortality, independently of HT and coronary artery disease (CAD) (11).

The pathogenesis of LVDD in diabetes is not completely elucidated. Various factors, some of which are directly related to diabetic metabolic disturbances, and others representing comorbidities such as obesity, HT or ischemic heart disease have been extensively investigated.

Diastolic dysfunction is currently evaluated according to the European Society of Cardiology Guidelines, using combined transmitral Doppler flow evaluation and tissue Doppler parameters. The variables recommended for identification of LVDD in patients with preserved LV ejection fraction are: septal e' <7 cm/sec, lateral e' <10 cm/sec, average E/e' ratio >14, left atrial volume index >34 mL/m², and peak tricuspid regurgitation velocity >2.8 m/sec. LVDD is present if more than half of these parameters meet the cutoff values mentioned above (12,13). Recently, other methods have been added, such as the

speckle tracking technique and magnetic resonance imaging, which allow determining early alterations of myocardial mechanics (14).

Treatment of LVDD in DM is complex, covering the suppression of associated risk factors (i.e. obesity, HT, dyslipidemia) and also the pathogenetic mechanisms involved in diabetic cardiomyopathy. Therapeutic methods include both lifestyle interventions and pharmacologic treatment (15). Physical exercise may have favorable effects not only on LVDD risk factors, but also on myocardial structure and function.

The aim of this narrative review is to synthesize the main pathophysiological processes and clinical features which characterize DM associated LVDD. Among treatment strategies, the therapeutic relevance of exercise training programs is emphasized.

Epidemiologic and clinical aspects

The evaluation of LV diastolic function has been investigated in both type 1 and type 2 diabetes mellitus using different non-invasive methods.

The development of diastolic function alterations has been reported in earlier stages of DM and even in prediabetic states, characterized by impaired glucose tolerance or insulin resistance. Celentano *et al.* compared normal glucose tolerance with impaired glucose tolerance and with type 2 DM patients, and found impaired diastolic function not only in subjects with DM, but also in those with impaired glucose tolerance, independently of possible confounding diseases, such as myocardial ischemia, obesity and blood pressure (16). Holzman *et al.* reported a continuous relationship between values of fasting plasma glucose and HbA1C and LVDD in a middle-aged non-diabetic population, suggesting early development of LV alterations even in prediabetic states (17).

In a large study, which investigated the relationship between glucose homeostasis and LV structure and systolic/diastolic function, glucose intolerance and insulin resistance were associated with measures of diastolic dysfunction even in stages preceding the development of DM (18).

In newly diagnosed (within 1 month) normotensive type 2 DM subjects aged between 30-60 years, LVDD was present in 41% of patients. The prevalence of LVDD increased with patients' age, being highest among subjects in the 50-60 years age group (66%). The great majority of the patients had evidence of grade I (delayed relaxation time pattern) LVDD. Another significant finding of this study was the association of glycosylated hemoglobin (HbA1C) with LVDD, suggesting the involvement of persistent hyperglycemia in diastolic function alteration (19). In young asymptomatic DM patients (mean age 29 years) without associated cardiovascular diseases, the prevalence of LVDD was 30% and an alteration of LV function was found even in subjects with less than 6 months diabetes duration. Women were twice more affected than men (10).

In a study that included 456 postmenopausal normotensive DM women who had had the disease for more than 5 years, the authors reported a higher prevalence of LVDD compared to controls. The presence of LVDD was associated with a BMI >30 kg/m^2 and with poor glycemic control, assessed by HbA1C >7.5% (20). Moreover, Leung *et al.* found that weight loss and improved glycemic control had additive beneficial effects on improving both diastolic and systolic LV functions in overweight patients with type 2 DM (21), suggesting a possible involvement of obesity and altered glycemic control in the development of myocardial changes. In order to evaluate whether DM per se, in the absence of arterial HT and CAD, affects LV structure and function, Loncarevic *et al.* compared four groups: group 1 - asymptomatic DM patients without HT and CAD, group 2 - DM patients with HT but without CAD, group 3 - DM patients with CAD and no HT and group 4 – healthy controls, using conventional and speckle tracking echocardiography. Their results indicated that cardiac structure alterations (increased LV mass, LV concentric remodeling, and left atrial enlargement) and impaired LV diastolic and systolic function were associated with the presence of DM independently of age, gender, BMI, HT and CAD. Asymptomatic DM patients without HT and CAD and preserved LV ejection fraction had increased LV mass associated with impaired LV systolic and diastolic function compared to controls (22). Diastolic dysfunction and cardiac hypertrophy, in the absence of CAD and HT, are considered two major characteristics of diabetic cardiomyopathy (23). However, a great number of DM patients, especially elderly diabetics, also have HT, a common cause of LVDD (24). The influence of DM and HT on LVDD was evaluated in a community based cohort, without overt cardiovascular disease. The results indicated that DM and HT had an independent negative effect

on LV diastolic function. When patients had both diabetes and HT, a higher LV end-diastolic pressure was found compared with either condition alone, suggesting an additional risk for the occurrence of LVDD in these patients compared to those with HT alone (25). Nevertheless, in patients without concomitant disease such as HT and CAD, followed up for 6 years, the authors reported that the prevalence of LVDD was relatively low, suggesting that in the early stage of LVDD, there may be a slow progression of myocardial changes (26).

Duration of diabetes, age and abnormally elevated levels of Hb1AC were independently correlated with LVDD in several studies (15,21,27,28,29). An independent relationship between LVDD and BMI was also reported (18,22,28). Other studies found no independent correlation between alteration of diastolic function and poor glycemic control (19,23).

Women seem to be more predisposed than men to develop LVDD (10,15,26). Moreover, in middle-aged and elderly Korean patients at risk of developing CAD, the correlation between metabolic syndrome components and LVDD was more pronounced in women than in men, suggesting a possible role of sex hormones in metabolic syndrome associated LV diastolic function alterations (30). Subclinical myocardial dysfunction was also identified in women with gestational diabetes, using speckle tracking echocardiography (31).

Pathogenesis

The pathogenesis of LVDD in patients with DM is complex and the mechanisms are largely intricated. Myocardial structure and function alteration may be caused by diabetes associated comorbidities or by diabetes specific metabolic or vascular dysfunctionalities.

Various causes may be involved in the development of LVDD in patients with DM, the most important being CAD and systemic HT. According to the Framingham study, CAD is twice more common in diabetic compared to non-diabetic subjects (32). Diabetes accelerates the development of atherosclerosis (5), while atherosclerotic CAD is a well known cause of LVDD. Coronary atheroma formation leads to coronary obstruction, plaque thrombosis and distal emboli with asymptomatic myocardial microinfarctions that may cause myocardial function alterations (33). Arterial HT, associated in more than 50% of patients with DM (34), induces LV hypertrophy and, subsequently LVDD.

Alteration of central arterial distensibility and development of arterial stiffness are common in diabetic patients. Arterial stiffness increases LV afterload and may contribute to LVDD (35). Increased circulating volume, due to sodium and water retention, and increased peripheral vascular resistance caused by insulin resistance and hyperinsulinemia may also induce LVDD (8).

In 1972, diabetic specific cardiomyopathy was described for the first time in four patients with diabetes and heart failure but without HT and coronary atherosclerosis, on histological examination of their hearts (36). Diabetic cardiomyopathy is suspected in clinically asymptomatic patients with LVDD. The pathogenesis of diabetic cardiomyopathy is not completely elucidated, but important metabolic and vascular alterations may be involved. One of them is the decrease of glucose metabolism causing stimulation of free fatty acids beta-oxidation (37,38). Another possible consequence of altered glucose metabolism is the accumulation of advanced glycation end products which affects calcium metabolism, favors apoptosis, with consequences on ventricular function (39). Hyperglycemia may activate the renin-angiotensin system, which stimulates oxidative stress, apoptosis and necrosis, with an increase in interstitial fibrosis (40). Both hyperglycemia and hyperinsulimenia may stimulate myocyte hypertrophy, which is accompanied, during evolution, by LVDD (18,41).

Cardiac microvascular disease in DM reduces coronary flow reserve, in the absence of atherosclerosis of epicardial coronary arteries (42), causing myocardial cell damage and subsequently, myocardial fibrosis (43). Histological examination of cardiac tissue has identified, in autopsy studies, more important interstitial and perivascular fibrosis in diabetics than in hypertensives. Fibrosis was even more pronounced when DM and HT were associated (44). The positive correlation between the duration of diabetes and the presence of LVDD suggests the involvement of microangiopathy and fibrosis in diastolic function alteration (11).

Autonomic dysfunction in DM patients may disturb autoregulation of coronary blood flow. A significant correlation between the severity of cardiac autonomic neuropathy and parameters of LV diastolic function has been reported in echocardiographic studies (45).

Vagal impairment leads to sympathetic overactivity which stimulates the renin-angiotensin-aldosterone system and heart rate, increases stroke volume and peripheral vascular resistance (45,46).

Systemic inflammation, in the presence of cardiovascular risk factors, may affect myocardial structure and function. The results of a prospective 4-year follow-up study showed that C-reactive protein predicted the development of LVDD in patients with type 2 DM (47).

Elevated levels of fasting triglycerides, frequently found in DM, may cause myocardial steatosis, a possible cause of left ventricular function alterations. In a prospective study, triglyceride levels were predictive for the development of LVDD in diabetes (8).

Obesity may be another important contributor to DM associated LVDD, via complex mechanisms including increased insulin resistance, systemic inflammation and oxidative stress, activation of the sympathetic nervous system and increased circulating blood volume (8).

Treatment strategies. Physical training as a therapeutic agent

Even though great progress has been made, treatment of LVDD in DM is still challenging because of the multiple comorbidities and complex mechanisms involved in its pathogenesis.

Treatment strategies

Therapeutic strategies include lifestyle measures and pharmacologic therapies.

Among lifestyle interventions, regular physical exercise and diet play an essential role, due to their immediate and long-term health advantages. Smoking cessation has additional benefits in preventing atherosclerotic vascular complications.

Pharmacologic treatment includes antidiabetic drugs, blood pressure and lipid lowering medication, and metabolic modulators.

Among antidiabetic drugs, metformin, thiazolidinedione, glucagon-like peptide, DPP-4, dipeptidyl peptidase and empagliflozin showed to have favorable effects on LV diastolic structure and/or function (49). Diabetes medication, along with diet, aimed at obtaining good glycemic control, is mandatory for all patients. In a 6-year prospective evaluation of diabetic patients with good glycemic, blood pressure and BMI control, LVDD developed in a small percent of patients and more than 50% of those with mild to moderate LVDD returned to normal diastolic function (50).

Treatment of HT with vasoactive medication, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta-blockers, improves symptoms and reduces mortality in DM patients with heart failure. Angiotensin II receptor blockers and angiotensin converting enzyme inhibitors (ACEI) may protect against ventricular fibrosis and alteration of diastolic function.

Treatment of hypercholesterolemia with statins reduces myocardial fibrosis and inflammation, improving LV function.

Metabolic medication such as trimetazidine and ranolazine showed to have favorable effects on endothelial function and myocyte calcium metabolism.

Novel medication includes antioxidants and cell- and genetic-based therapies.

All these medications have been recently reviewed and are beyond the scope of this article (8,49,51).

Exercise training in DM associated LVDD. Pathophysiological bases and clinical data

Exercise has been shown to improve glycemic control, reduce weight and blood pressure, and ameliorate vascular function and lipid profile (52).

Besides these positive effects on LVDD risk factors, a possible involvement in myocardial metabolism has been investigated. Moreover, extensive research is being carried out to elucidate the molecular mechanisms underlying the effects of exercise on LVDD in diabetic patients.

Both experimental and clinical studies have consistently shown that exercise may slow, or even regress, the development of diabetic cardiomyopathy. Decreased LV function, especially diastolic function, in a rat model of high-fat and high-sugar diet-induced diabetic cardiomyopathy was significantly improved after 8 weeks of aerobic and resistive exercise training (53).

In streptozocin induced diabetic cardiomyopathy, Woodiwiss *et al*. found increased myocardial stiffness caused by enhanced formation of myocardial collagen advanced glycosylation end products. Exercise attenuated the development of abnormal diastolic function without influencing the accumulation of advanced glycosylation end products, suggesting that exercise may influence active properties of the myocardium rather than its structure (54). In another study, exercise training was

initiated 3 weeks after the onset of diabetes and lasted for 4 weeks. The authors reported that exercise training may attenuate the perturbations in intracellular calcium metabolism in the diabetic myocardium (55). Amelioration of LVDD under physical exercise conditions has also been linked to a decrease in inflammatory and oxidative stress mediators, renin-angiotensin-aldosterone system activity and circulating catecholamines (56,57,58).

The advantages of physical training have been confirmed in several human studies. In a 3-year prospective study, 250 type 2 DM patients were randomized to a supervised exercise program, thought to provide at least moderate exertion, using a combination of both aerobic and resistance exercise, or to usual care. The results indicated that in 187 patients who underwent follow-up, an independent positive effect of the exercise program on the development or progression of abnormal diastolic function was found. Nevertheless, the intention-to-treat analysis was negative, which attested the difficulties of maintaining adherence to this form of therapy (59). Young female patients with type 1 DM, who underwent regular submaximal aerobic exercise over 20 weeks, presented clinically significant improvements in aerobic capacity and LV function. Ventricular function amelioration was the consequence of improved filling pressures and increased LV contractility (60). A study that included type 2 DM patients without coronary disease, having different degrees of LVDD, reported an improvement in exercise capacity and normalization of LVDD parameters after aerobic exercise training (3-month aerobic exercise using a cycle ergometer) (61).

Twenty-one men aged 49.8±1.7 years with type 2 DM and no previous history of cardiovascular disease participated in a soccer training group for 1 hour, twice a week. After 24 weeks, LV diastolic function parameters were improved and LV filling pressures decreased. At the same time, the results showed that soccer training increases exercise capacity and lowers blood pressure in men (62).

However, negative results were obtained in one study which included 48 men with type 2 DM (no more than 3 years after confirmation of DM), without known cardiac disease, randomized to supervised high-intensity training four times a week and standard therapy or to standard therapy alone for 12 months. The authors aimed to evaluate whether the reduction of risk factors ameliorates LV diastolic function. Despite a significant reduction of risk factors, particularly blood pressure, and improved diabetic control, exercise training did not influence LV filling pressures and myocardial deformation. The authors speculated that more intense and much longer exercise programs are needed to reduce myocardial alterations (63).

Even though the great majority of experimental and clinical studies indicate a beneficial effect of exercise training on LV diastolic function, large randomized control trials are required to confirm exercise efficacy and to establish the intensity and duration of the exercise programs.

Conclusions

Patients with DM have a significant risk of LVDD, which is associated with worse prognosis and increased mortality. The etiopathogenesis of LV diastolic abnormalities is complex and multifactorial, including diabetes comorbidities, such as HT, CAD, obesity and hyperlipidemia, as well as diabetic cardiomyopathy. Patients' age, diabetes duration, poor diabetes control and female gender may increase the risk of LVDD. Treatment strategies consist of lifestyle health patterns and pharmacologic treatment aimed at maintaining good glycemic control, normal blood pressure and plasma lipids. Physical exercise plays an important role, helping diabetic patients to better control cardiovascular risk factors. Experimental and clinical studies evaluating the effects of exercise on LVDD are encouraging, showing an amelioration of diastolic function parameters. However, large randomized controlled clinical studies are needed to better document and predict the favorable effects of exercise training on LVDD in diabetic patients.

Conflict of interest

The authors declare that there is no conflict of interest.

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Geothermal water for health state improvement: randomised controlled study

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Abstract

Introduction. Aim: to evaluate the effect of geothermal water of different mineralization on health state improvement.

Material and method. A randomized controlled single blinded parallel groups interventional study was performed. 250 participants were divided into 5 groups: 3 balneotherapy (20, 40 and 60 g/l total mineralization), 1 tap water, and 1 control group. Hydrotherapy was carried out on an outpatient on everyday basis for 5 days a week over a 2-week period. The main effect on health state was measured using SHSQ-25 questionnaire after 2 weeks and each month during 3-month follow-up period. Examination by a physician and common blood and urine tests were done after the treatment period.

Results and discussions. After a 2-week treatment, participants receiving all types of hydrotherapy showed a significant therapeutic response compared to the control group, especially in fatigue and mental state subcategories. The biggest total health enhancing effect after therapy was in seen in 40 g/l group, followed by 20 g/l group. The smallest effect was seen in tap water group. The most significant post-therapy effect during 3 months was given by 40 g/l procedures. Health self-rating after 2 weeks improved significantly only in geothermal water groups and lasted 2-3-month post-treatment. 2 weeks of balneotherapy had significant impact on Er, MCV, MCH, MPV, Eo, Tr, urine SG, and pH. According to the physician's assessment, the best results after 2 weeks were in 20 g/l group, but 40 and 60 g/l water procedures gave more residual effect.

Conclusions. The geothermal water of 40 g/l total mineralization has the best positive effect for health enhancement after 2 weeks and during 3-month period. 20 g/l water gives fast and short- term health effect, while 40-60 g/l water has long-lasting effect on health status.

Key words: *health status, balneotherapy, geothermal water, hydrotherapy*,

Introduction

In human beings health indicates the general condition of a person's mind, body and spirit. This usually means that an individual is free from illness, stress, injury or pain (1). Good health is the ability of a body to adapt to new threats and infirmities. A state of optimal health and well-being maximizes an individual's potential. Still, it is difficult to draw a line between health and illness, and dynamic transformational model was proposed - grey zone of subhealth (SHS) - the intermediate condition between health and illness that people pass through when they are becoming ill or regaining their health (2). Prevention and intervention strategies aimed at this zone are similar to the concept of preventive, predictive, and personalised medicine, which is an effective approach to the improvement of health, the prevention of disease and the treatment of an early-stage illness (2). The importance of timely prevention and early detection of disorders is increasing, as the global burden of disease is large. The measures for enhancing physical, intellectual, emotional, social, spiritual, and environmental well-being could prevent the burden of a disease and enhance the quality of life and productivity.

Already Asclepius and Hippocrates focused medical practice on the natural approach and treatment of diseases (3). Balneotherapy is one of the basic methods of treatment widely used in the system of natural medicine. It involves treating different health problems by bathing, usually in hot springs and other mineral-rich waters. The essence of balneotherapy effects is local changes caused by the direct influence of mechanical, thermal, and chemical factors through the skin and mucous membranes and the complex adjustment reactions as a result of neuroreflexive, humoral mechanisms, caused by stimulation of mechano-, thermo-, baro-, and chemoreceptors by biochemically active substances during a balneoprocedure (4). Balneotherapy has a scientific evidence-based effect on various systems of the body for a wide variety of theseverity of a disease and in subjects without major impairment: it promotes

active and healthy aging,improves immunity, impactspain, musculoskeletal, cardiovascular, respiratory, skin, mental health problems and quality of life (5-8). However, balneotherapy for psychosomatic conditions are still poorly investigated and there is still a lack of clear conclusion about its role in the disease prevention and treatment on what medicine of the 21st centurysuch rely as much as possible (9).

As early as the 5th century BC, the historian and physician Herodotus observed that different natural mineral springs in various parts of Greece had different therapeutic properties and he subsequently developed a rudimentary system for differentiating the therapeutic indications of various types of mineral waters. Hippocrates was also interested in the therapeutic properties of various waters, theorizing that their differing curative properties came from their differing contents of various minerals, like iron, copper, silver, gold or sulphur (10). Several models of salt water cutaneous adsorption/desorption and penetration of dissolved ions in mineral waters through the skin (osmosis and cell volume mechanisms in keratinocytes) were described and the role of these resources in stimulating cutaneous nerve receptors recently was examined (11).

There are many studies/reviews that have reported either physiological, or therapeutic, or the combination of both effects of balneotherapy on a particular system. However, we have not succeeded in finding a single report of balneotherapy's effect on the whole health status of the body. Also, there are no parallel group studies with the different total mineralization of mineral waters. These questions prompted us to do this particular study. The aim of our study was to evaluate the effect of geothermal water of different mineralization on general health status improvement.

Materials and methods

A randomized controlled single blinded (water type was known for researchers only) parallel groups interventional study was made during the period of May-September, 2018 in Klaipeda, Lithuania. Hydrotherapy procedures were carried out at the Rehabilitation Department of Klaipėda Seamen's Health Care Centre. The evaluation of participants' clinical statement at baseline, after 2 weeks of treatment and during the follow-up period was made at Klaipeda Science and Technology Park facility - Business incubator. Interventional study was implemented in observance of the rules of good clinical practice. The study was carried out with the authorisation of Kaunas Regional Biomedical Research Ethics Committee (permition No. BE-2-1). Inclusion criteria: current workers of 18-65 years of age with no history of clinically diagnosed disease, at least 2 symptoms of distress or symptom intensity more than 2 according to the general symptom distress scale (GSDS) or SHS according to SHSQ-25. Exclusion criteria were as follows: acute neurological deficit, epilepsy, inflammatory condition, cutaneous lesion, failure of respiratory, cardiovascular systems, kidney failure, unstable metabolic disorders, severe arrhythmia, febrile infections, bleeding, and pregnancy.

Participants

After completion of questionnaires 250 individuals were selected for the study. Coding and randomisation of the respondents were applied to avoid subjective influences. An individual who was not involved in the implementation of the study arranged randomization using a computer program. 5 groups of 50 individuals per group were randomly formed: 3 groups of baths of water of different mineralisation (20, 40, 60 g/l total mineralisation water), 1 group of pure water baths, and 1 control group (without treatment). All subjects were informed about the purpose, conditions, and course of the study prior to inclusion and signed a participant's agreement. Hydrotherapy was carried out on an outpatient on an everyday basis, for 5 days a week over a 2-week period, without changing their daily routines or going to work. The participants of the control group were not given any therapy and lived their usual life with no changes in their daily routine or work attendance. The protocol of the study required to participate in at least 60 per cent of the treatment procedures.

The sample size was estimated using the IBM SPSS Sample Power Release software v. 3 for the stress outcome using the general symptoms distress scale (GSDS). We examined mean differences between balneotherapy and the control groups. We estimated that the sample size in both groups should be 32 subjects, with the power of 81.7% to achieve a statistically significantly different result. This computation assumes that the mean difference in the general symptoms distress between the different

hydrotherapy and the control groups would be not less than 0.8, and the standard deviation within the groups would be 1.1. This effect was selected as the least significant effect of detectable importance; any smaller effect would not be of clinical or substantial significance. We assumed that the influence of balneotherapy and control group on the difference in the mean values of the variables is valid because such changes during the procedures are fully probable in this field of research. The mean difference of the observed variables of 0.8 (1.1) would be presented with a 95% CI of 0.25 to 1.35. Estimating the percentage of dropout, the total of 250 participants were taken.

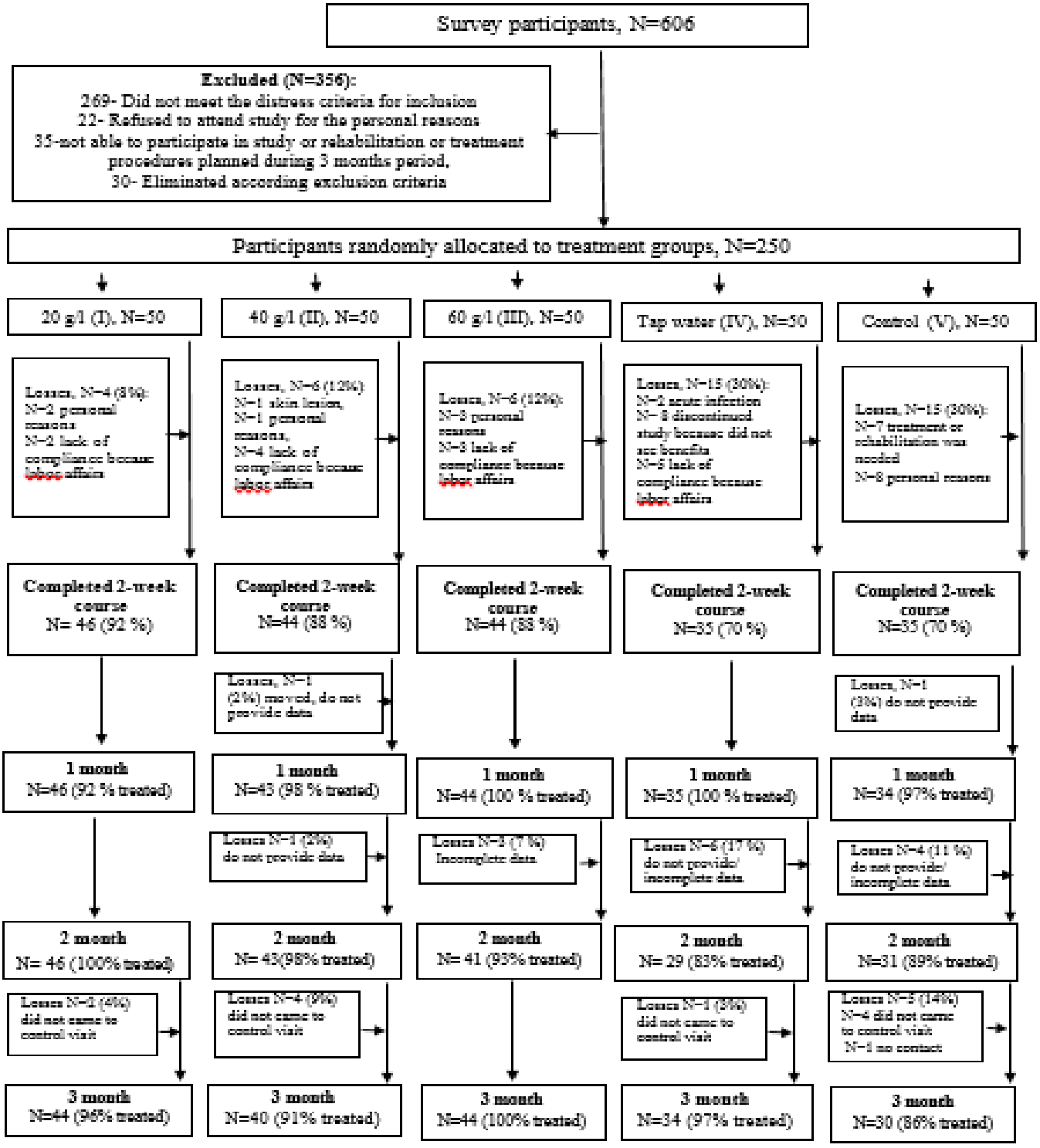

Fig. 1. Disposition of the study participants

The numbers of participants included in the analysis after treatment were as follows: total number 204 (81.6% survey participants): 46 from the geothermal group of 20 g/l total mineralization (I group), 44 in both 40 g/l (II group) and 60 g/l total mineralization (III group), and 35 in both- tap water (IV group) and control (V group). For the follow-up analysis 192 (76.8%) participants' data were taken.

Interventional procedure

Geothermal water used was highly mineralised (108 g/L) Na-Cl-Ca-Mg-SO4, pH 6.07) from Geoterma 2P (ID 25871) borehole (1135 m depth, lower Devonian layer (Devonian period started 350 million years ago and the minerals' age is about 1 million years). Water composition can be expressed by the Kurlov formula (eq./%):

$$M108.2\frac{Cl98}{Na64Ca24Mg12}.$$

Individual balneotherapy procedure was as follows: the bathtub was filled with 400 litres of geothermal water diluted with tap water up to the planned mineralisation. In accordance with calculations of dilution baths (400 l) were prepared as follows: 20 g/l (2%) bath was filled with 73 l of geothermal water and 327 l of pure tap water; 40 g/l (4%) - 145 l geothermal and 254 l of pure tap water; 60 g/l (6%) - 218 l geothermal and 181 l pure tap water (additional warmed in special heaters). The temperature of the baths was 36 °C. The participants had baths (immersing up to the armpits) for 20 minutes monitored by the trained personnel. Each participant was told to move slightly in the bathtub. Before, during and after the procedure, SpO2 and pulse were measured. After the procedure, it was recommended to the participants to rest in a prepared rest room and to consume fluids. After the baths, participants were recommended to gently dry the skin with a towel and not to shower for about one hour to prolong the effects of the procedure.

The geothermal water chemical composition in groups is shown in Table 1.

Table 1. *The mineral composition of geothermal water in groups*

Element, mg/l	I group	II group	III group
Cl	17110	25130	38400
SO4	526	735	1 160
HCO3	190	161	125
CO3	0,06	0.05	0.01
Na	7124	10550	16500
K	181	255	428
Ca	2500	3550	5110
Mg	659	940	1430
Fe	<0.01	<0.01	0.04
pH	7.28	7.27	6.72

Study outcome and research tools

The primary outcome was health status change after balneotherapy with geothermal water of different salinity in comparison with tap water and no treatment. Baseline, post-therapy (after 2 weeks) and follow-up (after 1, 2, 3 months after therapy) of health status was measured by the self-assessment scale sub-health status questionnaire(SHSQ-25) (13). SHSQ-25 includes 25 items on SHS and is targeted at physiological and psychological SHS. It is a reliable and valid instrument for measuring sub-health status. The range of the score of the SHSQ-25 is from 0 to 100 points. 0 points indicate the lowest level of SHS (good health) and 100 points indicate the highest level (poor health). Suboptimal health status is defined as the SHSQ-25 score above 35 points. The higher score of the SHSQ-25 one gets, the more severe his or her suboptimal health status is. The SHSQ-25 highlights the multidimensionality of SHS by encompassing the following domains: (1) fatigue, (2) the cardiovascular

system, (3) the digestive tract, (4) the immune system and (5) mental status. The SHSQ-25 is short and easy to complete, and, therefore, is an instrument suitable for use in both large-scale studies of the general population and routine health survey.

Subjective participant's health and wellness was assessed by 5-Likert's scale (1 - very good, 2 - good, 3 - satisfactory, 4 - bad, 5 - very bad). Overall body health state was assessed by a trained physician with the evaluation of objective body status as no change, better status, worse status, and complaints about health as no change, less complaints or more complaints.

Blood - complete blood count (CBC) - and urine tests were used to evaluate overall health: red blood cells (Er) - carry oxygen), haemoglobin (Hb) - oxygen-carrying protein in red blood cells),white blood cells (Leu) help to fight infection), platelets (Tr help with blood clotting) and other components (mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean platelets volume (MPV), leucocytes types), acidity (pH), urine specific gravity (SG).

Statistical Analysis

Data are reported as the mean ±SD for continuous variables, or as frequencies in the case of categorical variables. Descriptive statistics and univariate analyses were carried out using SPSS V23.0 (SPSS Inc., Chicago, Illinois, USA). Pearson $\chi 2$ tests and independent-sample t tests were used to compare the independent variables versus dependent variables. The hypothesis about the equality of probability distribution was checked against the Mann-Whitney-Wilcoxon U nonparametric criterion, and the corresponding 95 % CIs were calculated. Wilcoxon Sign, Kruscal Wallis nonparametric tests were used also; p value <0.05 was considered to be significant for all tests.

Results

The subjects' sociodemographic and health-related issues are shown in Table 2. All groups were similar concerning gender, marital status, working and resting hours, physical activity, alcohol consumption, stress intensity, wellness and health self-rating. The study was not homogenous with respect to the participants' education, age and smoking habit.

Table 2. *Sociodemographic and clinical characteristics of the participants in groups*

	I (N= 46)	II (N=44)	III (N=44)	IV(N=35)	V (N=35)	p
Age, N (%)	39.7 (10.5)	42.6 (10.4)	47.7 (9.5)	42.8 (12.8)	48.1 (12.0)	0.009
Gender, N (%)						
Men	4 (8.7)	7 (15.9)	7 (15.9)	4 (11.4)	7 (20)	0.638
Women	42 (91.3)	37 (84.1)	37 (84.1)	31 (88.6)	28 (80)	
Marital status, N (%)						
Prefer not to say	1 (2.2)	2 (4.5)				
Married	30 (65.2)	28 (63.6)	32 (72.7)	22 (62.9)	25 (71.4)	0.073
Single	11 (23.9)	8 (18.2)	4 (9.1)	7 (20)	3 (8.6)	
Divorced	4 (8.7)	6 (13.6)	4 (9.1)	6 (17.1)	3 (8.6)	
Widow			4 (9.1)		4 (11.4)	
Level of education, N (%)						
Incomplete secondary education	2 (4.3)	1 (2.3)				
Secondary	4 (8.7)	6 (13.6)	2 (4.5)	6 (17.1)	4 (11.4)	
Higher	7 (15.2)	3 (6.8)	3 (6.8)	3 (8.6)	11 (31.4)	0.004
High	1 (2.2)	6 (13.6)	3 (6.8)	2 (5.7)	2 (5.7)	
University	29 (63.0)	24 (54.5)	30 (68.2)	12 (34.,3)	13 (37.1)	
PhD	3 (6.5)	4 (9.1)	6 (13.6)	11 (31.4)	5 (14.3)	
Working hours per day, N (%)						
Less than 8	21 (45.7)	26 (59.1)	23 (52.3)	15 (42.9)	15 (42.9)	0.210

9 -12	20 (43.5)	14 (318)	15 (34.1)	14 (40)	18 (51.4)	
13-16	2 (4.3)	2 (4.5)	2 (4.5)	1 (2.9)		
More than 16		2 (4.5)	2 (4.5)		2 (5.7)	
Various	3 (6.5)		2 (4.5)	5 (14.3)		
Resting hours per day, N (%)						
Less than 6	11 (23.9)	7 (15.9)	4 (9.1)	7 (20)	6 (17.1)	
7 – 8	25 (54.3)	23 (52.3)	20 (45.5)	15 (42.9)	18 (51.4)	0.067
9 – 10	8 (17.4)	8 (18.2)	14 (31.8)	8 (22.9)	1 (2.9)	
More than 10	2 (4.3)	5 (11.4)	6 (13.6)	5 (14.3)	10 (28.6)	
Various		1 (2.3)				
Smoking, N (%)						
Everyday	4 (8.7)	3 (6.8)	3 (6.8)		1 (2.9)	
Often		3 (6.8)				0.041
Occasionally	7 (15.2)	2 (4.5)	2 (4.5)	1 (2.9)	4 (11.4)	
Never	35 (76.1)	36 (81.8)	39 (88.6)	34 (97.1)	30 (85.7)	
Alcohol use, N (%)						
Everyday				2 (5.7)		
2-3 time/week	14 (30.4)	2 (4.5)	4 (9.1)		4 (11.4)	
Once per week	3 (6.5)	7 (15.9)	3 (6.8)	7 (20)	5 (14.3)	0.124
2-3 time/month	18 (39.1)	16 (36.4)	11 (25)	10 (28.6)	12 (34.3)	
Few time per year	6 (13.0)	11 (25)	22 (50)	9 (25.7)	12 (34.3)	
Never	5 (10.9)	8 (18.2)	4 (9.1)	7 (20)	2 (5.7)	
Physical activity, N (%)						
Everyday	6 (13.0)	7 (15.9)	5 (11.4)	3 (8.6)	4 (11.4)	
4-6 times/week	1 (2.2)	8 (18.2)	1 (2.3)		3 (8.6)	
2-3 times/week	13 (28.3)	11 (25)	16 (36.4)	13 (37.1)	17 (48.6)	0.080
Once per week	6 (13.0)	8 (18.2)	4 (91)	6 (17.1)	3 (8.6)	
2-3 times/month	7 (15.2)	3 (6.8)	6 (13.6)	3 (8.6)	2 (5.7)	
Few times/year	5 (10.9)	4 (9.1)	5 (11.4)	7 (20)	4 (11.4)	
Never	8 (17.4)	1 (2.3)	7 (15.9)	3 (8.6)	2(5.7)	
Stress intensity, N (SD)	6.72 (2.37)	6.6 (1.95)	6.55 (2.28)	5.71 (2.38)	6.26 (1.9)	0.285
Wellness, mean rank*	113.76	101.43	98.68	97.07	99.27	0.579
Health, mean rank*	104.92	108.66	100.17	97.56	99.44	0.878

* Kruscal Wallis test

The change of health state

After 2-week treatment, participants receiving hydrotherapy (geothermal and tap water) showed a significant therapeutic response compared to the control group (Table 3). No significant change was seen in the control group. The biggest health enhancing effect after therapy was in seen in II (40 g/l) group (mean difference 11.1, p <0.001), followed by I (20 g/l) group (mean difference 9.1 (p<0.001). The smallest effect was seen in IV (tap water) group (mean difference 6.6, p<0.001). The significant post-therapy positive effect remained all 3 months in all hydrotherapy groups, with the biggest health state change in II (40 g/l) group.

The biggest changes after 2 weeks were seen in fatigue and mental status subscales. Significant positive changes for all subscales were made by 40 and 60 g/l geothermal water baths, and significant negative change for digestive tract was in the control group. Changes in 20 g/l and tap water groups for digestive tract were insignificant. 20 and 40 g/l geothermal water procedures reduced fatigue almost equally (4.2, p<0.001 and 4.1, p<0.001). Mental status most improved by 40 g/l geothermal water procedures (3.3, p<0.001), followed by 20 g/l procedures (2.7, p<0.001). Positive effect on the immune system was in all hydrotherapy groups (biggest in 40 g/l group (1.5, p<0.001), smallest in tap water group (1.1, p<0.001). A similar positive effect on the cardiovascular system was given by all hydrotherapy types. The best result for digestive tract was achieved in 40 g/l group (1.5, p<0.001), and 60 g/l (0.5, p=0.011) groups. No positive change in any subscale was seen in the control group.

The feeling of wellness after 2 weeks was better in all geothermal and control groups and remained better than baseline after 3 months in 20 and 40 g/l groups (Table 4). Health rating after 2 weeks enhanced significantly only in geothermal water groups; 20 and 60 g/l water procedures effects lasted 2-month, but 40 g/l all 3-month follow-up period.

Table 3. *The change of health state in groups during study period*

Groups		Mean (SD)	Mean difference (CI lower- upper)	p
I	Before	27.24 (10.69)		
	After 2 w.	18.17 (10.26)	9.07 (5.96 to 12.17)	<0.001
	After 1 mo.	15.17 (9.56)	12.07 (9.48 to 14.66)	<0.001
	After 2 mo.	15.07 (8.59)	12.17 (8.95 to 15.40)	<0.001
	After 3 mo.	17.61 (9.76)	9.98 (6.29 to 13.66)	<0.001
II	Before	25.86 (12.06)		
	After 2 w.	14.80 (6.84)	11.07 (7.57 to 14.57)	<0.001
	After 1 mo.	12.42 (7.47)	13.58 (10.11 to 17.05)	<0.001
	After 2 mo.	13.40 (8.3)	12.79 (8.97 to 16.61)	<0.001
	After 3 mo.	13.68 (9.63)	12.29 (8.57 to 16.01)	<0.001
III	Before	23.32 (9.95)		
	After 2 w.	15.82 (7.80)	7.5 (4.57 to 10.43)	<0.001
	After 1 mo.	14.61 (8.26)	8.70 (5.94 to 11.47)	<0.001
	After 2 mo.	14.05 (10.32)	8.46 (5.04 to 11.89)	<0.001
	After 3 mo.	14.05 (8.79)	9.27 (6.29 to 12.25)	<0.001
IV	Before	23.80 (13.41)		
	After 2 w.	17.17 (10.08)	6.63 (3.89 to 9.37)	<0.001
	After 1 mo.	17.23 (11.73)	6.57 (2.95 to10.20)	0.001
	After 2 mo.	14.10 (10.26)	10.07 (5.81 to 14.32)	<0.001
	After 3 mo.	17.12 (11.78)	6.56 (3.09 to 10.03)	0.001
V	Before	16.71 (7.31)		
	After 2 w.	16.06 (6.09)	0.66 (-1.32 to 2.63)	0.503
	After 1 mo.	13.68 (5.66)	2.79 (0.66 to 4.92)	0.012
	After 2 mo.	12.19 (6.13)	4.77 (2.15 to 7.40)	0.001
	After 3 mo.	12.73 (6.86)	3.30 (0.96 to 5.64)	0.007

The changes in SHSQ-25 subscales in all study groups after treatment period are shown in Figure 2.

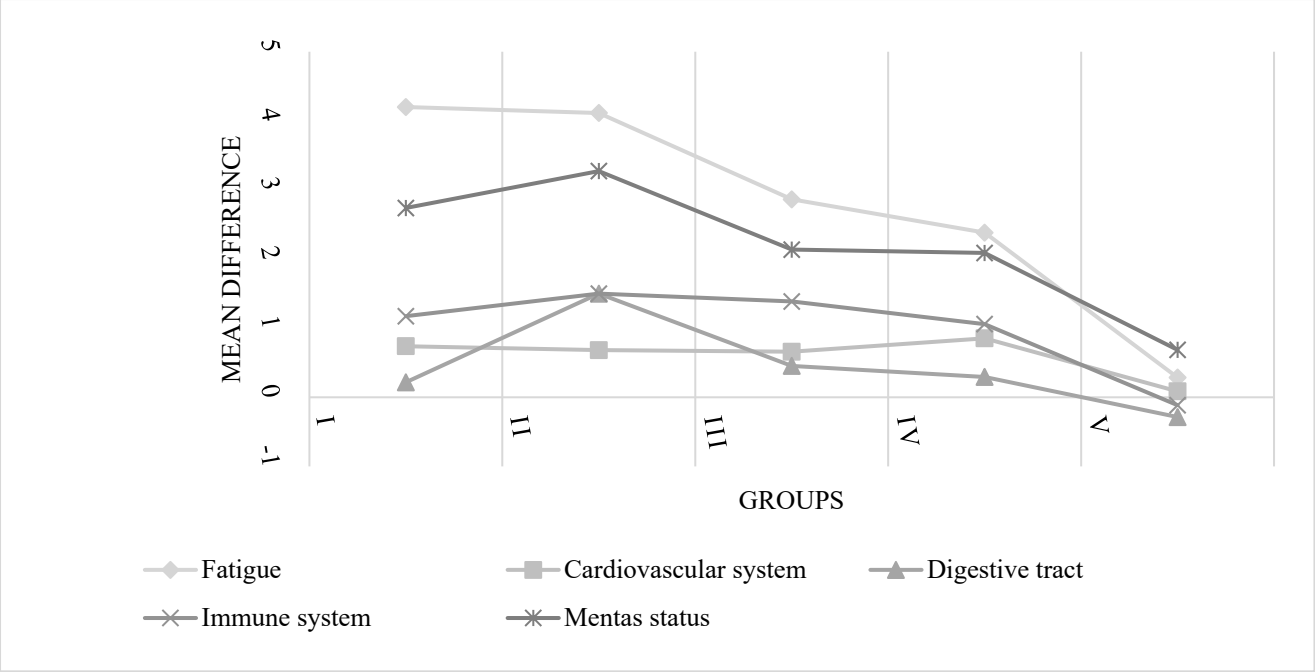

Fig. 2. Health subscales change in groups after 2-weeks treatment

Table 4. *Wellness and health rating change in groups during study period*

		I		II		III		IV		V	
		Z	Asymp. Sig. (2-tailed)	Z	Asymp. Sig. (2-tailed)	Z	Asymp. Sig. (2-tailed)	Z	Asymp. Sig. (2-tailed)	Z	Asymp. Sig. (2-tailed)
Wellness	2 weeks	-4.746	0.000	-4.062	0.000	-3.019	0.003	-0.905	0.366	-3.207	0.001
	1 mo	-4.004	0.000	-2.742	0.006	-2.696	0.007	-1.428	0.153	0.001	0.046
	2 mo	-2.846	0.004	-3.617	0.000	-1.968	0.049	-2.307	0.021	-2.840	0.005
	3 mo	-3.400	0.001	-3.622	0.000	-1.927	0.054	-1.937	0.053	-1.485	0.138
Health	2 weeks	-3.175	0.001	-3.989	0.000	-2.400	0.016	-1.897	0.058	-1.732	0.083
	1 mo	-2.858	0.004	-3.133	0.002	-2.000	0.046	-1.807	0.071	-1.807	0.071
	2 mo	-2.352	0.019	-2.294	0.022	-2.065	0.039	-2.798	0.005	-1.604	0.109
	3 mo	-1.633	0.102	-3.892	0.000	-1.593	0.111	-1.784	0.074	-1.232	0.218

a. Wilcoxon Signed Ranks Test

Based on positive ranks

The change in laboratory findings

After 2 weeks there were only some significant changes in laboratory findings (Table 5): 20 g/l mineralisation baths lowered Er and elevated MPV; 40 g/l water baths elevated Er and Tr and lowered MPV; 60 g/l water baths lowered MCV, MCH, and urine SG, also elevated blood eosinophils (Eo), urine pH (less acidic). Tap water baths group showed lowered MCV, elevated Tr, lymphocytes (Lym) and monocytes (Mo). There were significantly elevated Eo, Er and Hb, lowered MPV and MCV in the control group.

Table 5. *Changes of CBC and urine after 2 weeks in study groups*

Parameter	Group	Mean difference	SD	CI lower	CI upper	T	p
ER	I	0.10	0.25	0.0230	0.1705	2.642	0.011
	II	-0.08	0.26	-0.1643	-0.0041	-2.120	0.040
	III	-0.06	0.20	-0.1211	0.0015	-1.967	0.056
	IV	-0.02	0.19	-0.0887	0.0512	-0.547	0.588
	V	-0.12	0.18	-0.1979	-0.0413	-3.166	0.004
MCV	I	-0.06	1.01	-0.3568	0.2438	-0.379	0.706
	II	0.30	1.07	-0.0284	0.6284	1.844	0.072
	III	0.82	0.86	0.5545	1.0774	6.294	<0.001
	IV	0.37	0.93	0.0354	0.7021	2.256	0.031
	V	0.38	0.81	0.0331	0.7321	2.270	0.033
MCH	I	-0.29	1.33	-0.6871	0.1002	-1.502	0.140
	II	0.03	0.31	-0.0656	0.1260	0.637	0.528
	III	0.24	0.27	0.1539	0.3188	5.782	<0.001
	IV	0.09	0.38	-0.0430	0.2305	1.398	0.172
	V	-0.11	0.44	-0.2985	0.0811	-1.188	0.248
HB	I	1.52	5.96	-0.2487	3.2922	1.731	0.090
	II	-1.65	5.64	-3.3867	0.0844	-1.920	0.062
	III	-0.61	5.82	-2.3842	1.1570	-0.699	0.488
	IV	-0.19	6.10	-2.3862	2.0112	-0.174	0.863
	V	-3.83	4.97	-5.9750	-1.6771	-3.692	0.001
TR	I	-2.35	91.94	-29.64910	24095344	-0.173	0.863
	II	-7.93	23.54	-15.17466	-0.68580	-2.209	0.033
	III	0.73	32.60	-9.18317	10.63772	0.148	0.883
	IV	-13.06	31.92	-24.56987	-1.55513	-2.315	0.027
	V	-4.70	17.09	-12.08671	2.69541	-1.318	0.201
MPV	I	-0.19	0.45	-0.3244	-0.0582	-2.895	0.006
	II	0.20	0.43	0.0677	0.3323	3.051	0.004
	III	0.04	0.36	-0.0701	0.1474	0.716	0.478
	IV	-3.06	17.22	-9.3725	3,2563	-0.989	0.331
	V	0.19	0.28	0.0672	0.3067	3.239	0.004
LEU	I	0.17	1.18	-0.18505	0.5177	0.953	0.346
	II	0.20	1.29	-0.19832	0.5969	1.012	0.318
	III	0.13	0.98	-0.16905	0.4291	0.877	0.386
	IV	-0.14	0.58	-0.34806	0.0724	-1.337	0.191
	V	0.05	0.87	-0.32665	0.4258	0.273	0.787
NEU	I	0.03	0.98	-0.26312	0.3262	0.216	0.830
	II	0.22	1.49	-0.24339	0.6820	0.957	0.344
	III	0.14	0.76	-0.09042	0.3774	1.238	0.223
	IV	0.05	0.47	-0.13273	0.2258	0.532	0.599
	V	0.05	0.71	-0.25903	0.3538	0.321	0.751
LYM	I	0.16	0.63	-0.03103	0.3497	1.687	0.099
	II	0.03	0.29	-0.05712	0.1238	0.744	0.461
	III	-0.04	0.43	-0.17234	0.0947	-0.587	0.560
	IV	-0.12	0.24	-0.20850	-0.0246	-2.597	0.015
	V	0.30	0.85	-0.06865	0.6678	1.687	0.106
MON	I	0.01	0.10	-0.01891	0.0416	0.755	0.454
	II	0.00	0.11	-0.02993	0.0385	0.253	0.802
	III	0.01	0.12	-0.02127	0.0501	0.815	0.419
	IV	-0.04	0.06	-0.06160	-0.0129	-3.132	0.004
	V	-0.00	0.11	-0.04746	0.0440	-0.079	0.938
EO	I	-0.02	0.24	-0.09119	0.0507	-0.574	0.569
	II	-0.19	1.05	-0.51792	0.1394	-1.163	0.251
	III	-0.03	0.08	-0.0540	-0.00415	-2.354	0.023
	IV	-0.02	0.10	-0.0571	0.01641	-1.134	0.267
	V	-0.03	0.06	-0.0576	-0.00766	-2.710	0.013
SG	I	0.24	7.41	-2.0956	2.5834	0.211	0.834
	II	1.58	8.94	-1.3586	4.5165	1.089	0.283
	III	7.22	9.39	0.0035	14.4409	2.307	0.050
	IV	2.14	9.14	-3.1337	7.4194	0.877	0.396

	V	0.28	8.82	-4.1102	4.6658	0.134	0.895
pH	I	0.01	0.75	-0.2258	0.2502	0.104	0.918
	II	-0.24	0.78	-0.4924	0.0187	-1.878	0.068
	III	-0.61	0.78	-1.2120	-0.0102	-2.345	0.047
	IV	-0.07	0.62	-0.4269	0.2841	-0.434	0.671
	V	0.08	0.77	-0.3004	0.4671	0.458	0.653

According to the physicians' clinical assessment of participants' health, the highest percentage of improved health status after 2-week treatment was in 20 g/l water group (94 %), and remain better after 3-month period in 60 g/l water group (91 %); less complains after 2 weeks were expressed by participants of 20 g/l group (100 %); positive change remained after 3 months in 40 and 60 g/l groups (93 %) (Figure 3). Less than 9 % of participants showed better health status after treatment and for more than one third (34 %) assessment was better than at baseline after 3 months. Assessment of the control group showed no changes in health status and complaints after 2 weeks, but better health status (17 %) and less complaints (9 %) were after a 3-month period.

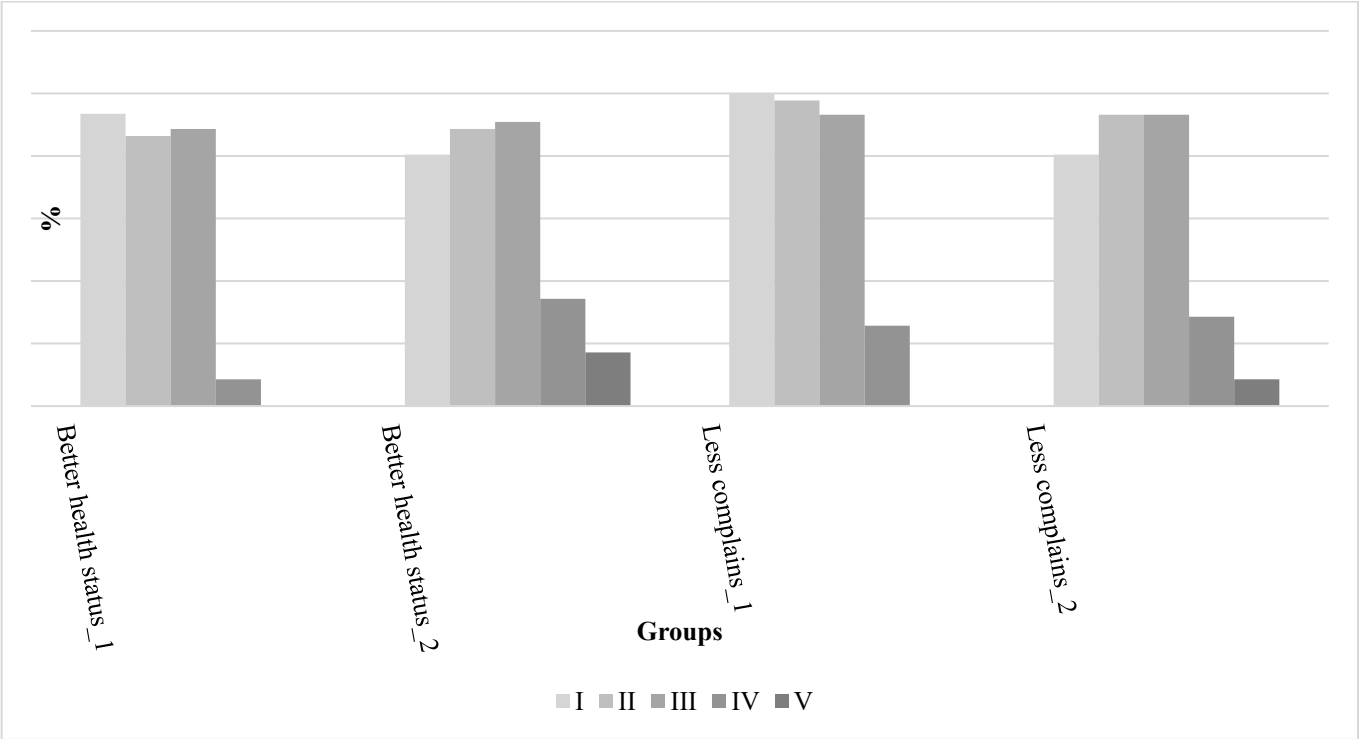

Fig. 3. Physicians' assessment of changes after 2-week and at 3-month period in study groups

Discussion

The results of the study demonstrated that the 2-week hydrotherapy with geothermal water of different total mineralisation and warm tap water had a significant positive effect on health status. All positive effects of geothermal water baths were greater than with tap water. The significant positive results in the control group were minimal - only in wellness and some laboratory findings.

Assessing changes in SHSQ-25, the best significant total positive result for health enhancement after the 2-week and 3-month follow-up was in the 40 g/l geothermal group. According to the health subscales most affected were fatigue and mental status in all hydrotherapy groups. The geothermal water of 20 and 40 g/l total mineralisation best suits for fatigue management, 40 g/l for mental status, immunity, digestion correction, and 20 g/l and tap water for cardiovascular problems.

The feeling of wellness was most evident with the geothermal water bath, especially 20 g/l mineralisation with the significant residual effect of 3 months in 20 and 40 g/l groups. Health rating was significantly better in geothermal groups with the best after treatment and 3-month period in 40 g/l group.

Blood and urine laboratory tests did not show any special results. 2 weeks of balneotherapy had some impact on Er, MCV, MCH, MPV, Eo, Tr, urine SG and pH. Some similar changes were observed in the tap water (MCV, Tr) and control (Er, Eo, MPV, MCV) groups. Tap water made some significant changes in leukocytes types (lym., mon). MPV is a good indicator of the activity of thrombocytes which increases with the presence of emotional stress, is also a trigger of coronary events (14), so positive effect could be counted with 40 g/l water procedures (elevated Tr could be reactive because of the redistribution of Tr in the organism after procedures such as physical exercise). An explanation for the lowering of MCV and MCH after 60 g/l water procedures could be an acquired state where boosted metabolism reactions could take place (Er mitosis acceleration) as Er and Hb were growing insignificantly (except in the 20 g/l group). The lowering of SG after the 60 g/l water procedures shows decreased concentric function of the kidneys or lowered antidiuretic hormone secretion producing the diuretical effect. The change of urine pH shows change in acid-alkaline balance to alkalinizing side due to the diuretical effect or elevated alkaline elements in urine (15). These changes suggest that geothermal water of bigger mineralisation is more metabolically active and could be responsible for longer residual effects on the body.

According to the physicians' assessment the best results after 2 weeks were in the 20 g/l group, but 40 and 60 g/l water procedures had more residual effects. Our findings on geothermal water effect can be associated with other researchers' description of saline water (counteract gastric problems, increase cutaneous circulation, reduce inflammation of inflammatory and peripheral nervous system disorders), sulphated water (as a detoxicating agent, reducing gastric secretions), alkaline waters with bicarbonates, calcium, magnesium, potassium (stimulate bile, pancreas, intestines and phlegm secretion, alkalize the urine and the blood) (10). Saline water therapeutic agents have been described to act via mechanical, thermanl, and chemical mechanisms (11).

Our finding of best effect for health status of 40 g/l geothermal water procedures meets with the Lithuanian recommendations to use 20–40 g/l water for optimal treatment of disorders (16). The scientific literature from 2002 to 2013 has shown that health resort medical treatment is associated with clinical improvement in the diseases of the skin, respiratory, circulatory, digestive and nervous systems, cancer, nutritional and metabolic disorders, mental disorders, diseases of the ear, endocrine diseases, female genital diseases and nutritional deficiencies (17). Scientists believe that mineral water treatment methods compared to non-mineral similar treatments had better and longer improvements in pain, function, quality of life, clinical parameters, and others (18).

Our study about the effect of balneotherapy on the general health status using SHSQ-25 was done for the first time. Therefore we cannot compare the effect of geothermal water baths in terms of effect size? After Yang balneotherapy intervention, sleep disorders, mental stress and problems of general health (head, joint pain, leg or foot cramps, and blurred vision) were relieved significantly as compared with the control group. Fatigue, eye tiredness, limb numbness, constipation, skin allergy and women's health problems were relieved significantly in the self-comparison of the intervention group, but not between the two groups. All indications (except for bad mood, low mood, and worry or irritability) in the intervention group significantly improved, with the effect size from 0.096 to 1.302. Multiple logistic regression analysis showed that the frequency, length, and location of balneotherapy in the intervention group were the factors influencing emotion, sleep, and health condition (19).

Our previous clinical study demonstrated the positive impact of balneotherapy with 108 g/l mineralisation geothermal water on distress; it provided positive preventative results: the reduction of health risks and the growth of health recourses. The probability of distress-induced general health deterioration decreased by 18 %; also, favourable effects of balneotherapy using geothermal water on pain, sleep disturbances and intestinal problems were observed (9). Large effect sizes between geothermal water treatment versus control were found in lowering general fatigue (1.06, 95% CI −1.47 to −0.65) and in activity (−0.89, 95% CI −1.29 to −0.48), and mood (1.16, 95% CI 0.74 to 1.57); a medium effect size was seen in reducing physical (0.73, 95% CI 1.13 to −0.34) and mental fatigue (0.53, 95% CI −0.92 to −0.14) and increasing motivation (0.65, 95% CI −1.04 to −0.25) (20). Blasche G 3-week spa therapy (carbonated mineral water, hot mud packs, tub bath) study with actively working individuals also showed

change in fatigue, distress, reduced motivation, and quality of sleep (burnout symptoms). This improvement was sustained up to 3 months (21). The Dubois O study results demonstrate that balneotherapy was statistically superior to paroxetine in terms of the primary efficacy criterion: HAM-A total score (mean diff −3.7, psychic: 8 weeks −1.6, somatic −2.1, p<0.001 (22).

There are separate studies and meta-analyses of hydrotherapy for the treatment of fibromyalgia syndrome. Moderate-to-strong evidence for a small reduction in pain with regard to hydrotherapy and moderate-to-strong evidence for a small improvement in health-related quality of life by HRQOL with no effect for depressive symptoms were observed, but balneotherapy showed moderate evidence for a medium-to-large size reduction in pain and moderate evidence was given for a medium improvement of HRQOL (SMD −0.78; 95% CI [−1.13, −0.43]; $P < 0.0001$; $I^2 = 0\%$). Counteracting with our general mental status improvement findings, significant effect on depressive symptoms was not found (7). Antonelli's study with knee osteoarthritis also proved that balneological interventions compared to standard treatment result in better long-term overall QoL [ES = - 1.03 (95% CI - 1.66 to - 0.40)], pain improvement (23). It has been proven that Dead Sea and Hungarian mineral waters balneo- and climatotherapy decreasse pain, improve joint function and quality of life in rheumatoin arthritis, in ankilosing spondylitis, as well as in psoriatic arthritis, and in osteoarthritis (7, 24) as well as for fibromyalgia SF-36 variables as mental health (from 51 to 70) after treatment, vitality (from 39 to 59), body pain (from 19 to 39), also severity of fatigue (from 65 to 43, VAS), general well-being (from 66 to 48), psychological well-being (anxiety, depresion) were alleviated (25). In Ozkurt's study balneotherapy was found to be superior than control in terms of pain intensity, FIQ, Beck Depression Inventory, patient's global assessment, investigator's global assessment scores, and tender point count. This lasted up to 3rd month, except for the Beck Depression Inventory score and the investigator's global assessment score (26). In Baysal's study the most common benefits observed by the participants of balneotherapy treatment were muscle loosening (66.8%), reduced pain (50.7%) and relaxation-rest (49.2%). A large majority of the participants (95.5%) stated that they would recommend balneotherapy to others (27).

We have not found any significant effect on white blood cells in geothermal water groups, but in warm tap water group lymphocytes and monocytes were elevated. This is in line with Kuehn study of cold water therapy in cancer patients results where significant increases in post-treatment neutrophils, lymphocytes, and monocyteswas observed. Blazickova study results were as follows: the whole-body hyper thermic water bath increased relative CD8+ lymphocyte, NK cell counts and their activity (which were probably dependent on the increased somatotropic hormone). This contradictsDigiesi study where head-out water immersion for 30 min decreased blood viscosity and Er but without significant changes in Leu and Tr count and MCV (5). Good health is central to handling stress and living a long and active life.It may not be possible to avoid disease completely, but doing as much as we can to develop resilience and prepare the body and mind to deal with problems as they arise is a step we can all take.

We should incorporate all possible aspects of medicine including non-pharmacologic approaches in order to maintain health and prevent NCDs. These approaches include hydrotherapy and balneotherapy which can be of great importance if health promotion strategies are considered and if the FEMTEC concept is followed. This concept was developed by Santuari and Solimene who propose to focus on prevention and health promotion rather than on the concept of cure (28).

Limitations and strengths of study

Differences of some sociodemographic parameters among the groups (the fact that in the course of the study we lost younger study participants), the timing of the study (summer, people being on holidays and resting) might have given reliable positive changes among the control group participants. Addition of aromatic oils when preparing pure water baths might have had additional impact on better results. Preparation of individual baths might have caused small deviations from planned mineralisations. Since there are no standardised protocols for the study of concrete influence it is complicated to draw final conclusions and compare our results with those of other studies. We agree that to account for placebo effects, double-blind trials are best, but it is difficult to prepare such conditions as it is easy to distinguish

between the organoleptic characteristics of mineral water and control treatments with fresh water.
Strengths of our study: comparison of different total mineralisation waters in parallel groups, control with tap water and no treatment, investigating balneotherapy effects on people without disease to find preventative measures or strengthen body health. This allows to offer recommendations how to apply certain procedures to guarantee a person's physical and psychological well-being.

Conclusions

- Two- week hydrotherapy has a significant positive effect on health status, especially fatigue and mental subscales.
- Effects of geothermal water baths are greater than with tap water.
- The geothermal water of 40 g/l total mineralisation has best positive effect on health enhancement after 2 weeks and after a 3-month follow-up.
- 20 and 40 g/l total mineralisation best suits for wellness and fatigue management, 40 g/l - for mental status, immunity, digestion correction, and 20 g/l and tap water - for cardiovascular problems.
- 20 g/l water gives fast and short-term health effect, while 40-60 g/l water has long-lasting effect on health state.

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Conflict of interest statement: None declared.

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Balneotherapy treatment for patients suffering from low back pain

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Abstract

Nowadays, a significant number of people experience low back pain during his lifetime. The causes are not clear at all, but several studies attribute this musculoskeletal disease to economical and psychosocial factors. Among all the treatments proposed, this study focuses in balneotherapy. The search in Medline Database through PubMed, PEDro and Cochrane Library, has yielded some interesting results. Consulted bibliography show that balneotherapy may be effective in the treatment of low back pain, but there are not so many correctly-designed studies to affirm this fact with evidence.

Key words: *balneotherapy, low back pain, medicinal water, mud therapy*,

1 Introduction

Low back pain is an extremely common problem that most people experience at least once in their life (1). The prevalence of suffering low back pain increases linearly from the third decade of life on, until the 60 years of age, being more prevalent in women (2).

Leaving aside serious medical or psychological conditions and according to International Statistical Classification of Diseases and Related Health Problems (ICD), there are different categories: low back pain, lumbago, lumbosacral segmental/somatic dysfunction, low back strain, spinal instabilities, flatback syndrome, lumbago due to displacement of intervertebral disc, lumbago with sciatica (3).

The Orthopaedic Section of the American Physical Therapy Association (APTA) affirms that current literature does not support a definitive cause for initial episodes of low back pain. Risk factors are multi-factorial, population specific, and only weakly associated with the development of low back pain (3). Despite this, several studies attribute low back pain to economical factors as income levels per capita, psychosocial factors like work-family imbalance, exposure to hostile work, job insecurity, long work hours and certain occupation groups (4, 5, 6, 7). The 6 European Working Conditions Survey showed that the percentage of workers who feel some pain derived from the postures or efforts made at work was 77,5%. The main location of pain was low back with 44,9% of all participants, followed by neck pain with 34,3%. The survey also affirmed that an important percentage of workers of transportation and storage sector (53,7%) construction sector (52,5%) and health and social activities (52,2%) referred low back pain (8). Low back pain has some consequences, as it is associated with short sleep duration and poor sleep quality (9).

It is the number one cause of dissability (10). Although people don't die from low back pain, the morbidity toll is enormous from both personal and societal perspectives. It is reported by more patients and has a higher impact in the workforce, as well as financially, than any other musculoskeletal disorder and most other clinical conditions (11). The trend to suffer low back pain is upward. Freburger, et al demonstrated an increase in chronic low back pain from 3.9% in 1992 to 10.2% in 2006 in a telephone survey of North Carolina households (12).

Because non-specific low back pain does not have a known pathoanatomical cause, treatment focuses on reducing pain and its consequences (13). The treatment includes pharmacological and nonpharmacological therapies (psychological therapies, multidisciplinary rehabilitation, spinal manipulation, acupuncture, massage, exercise and related therapies, and various physical modalities) (14).

Balneotherapy is the treatment of disease by bathing in thermal spring water (15). It is based on the buoyancy, physical properties, temperature, and chemical effects of mineral water (16). Mud is a heated slurry, which is the result of the combination of solid material (mainly clay) and mineral water, used for external application after an adequate maturation period, at a temperature between 45°C and 50°C (17). The aim of this review is to analyze if balneotherapy is an effective treatment for low back pain.

2 Methods

The search was carried out in different databases. The search strategy varied according to each database:
Medline Database through PubMed: The search was made the 30 of January 2019.

1. Terms search: "balneotherapy", "low back pain". 53 results were found.
2. The publication dates were changed to 10 years, and the search was restricted to human species. 25 results were found.
3. The abstracts were read to select the potentially interesting articles.
4. Another search was made with the terms: "mud", "low back pain". 13 results were found.
5. The publication dates were changed to 10 years, and the search was restricted to human species. 7 results were found.
6. They were selected the articles according to this study.

PEDro: The search was made the 5 of February 2019.

1. Advanced search: "Balneotherapy low back pain"
2. Therapy: hydrotherapy, balneotherapy
3. Body part: lumbar spine, sacro-iliac joint or pelvis
4. Published since: 2009
5. 5 records were found. The abstracts were read to select the interesting results.
6. Advanced search: "Mud low back pain"
7. Therapy: hydrotherapy, balneotherapy
8. Body part: lumbar spine, sacro-iliac joint or pelvis
9. Published since: 2009
10. 2 records were found. The abstracts were read to select the interesting ones.

Cochrane Library: The search was made the 5 of February 2019.

1. Advanced search with the terms: "Balneotherapy" AND "low back pain"
2. The search was limited to the last ten years.
3. 10 essays were found. The abstract determined which ones were chords to the study.
4. Advanced search with the terms: "Mud therapy" AND "low back pain"
5. The search was limited to the last ten years.

Only 2 essays were found. The reading of the abstract concluded in the selection of the appropriate.

3 Results

Table 1. Effectiveness of balneotherapy in low back pain.

4 Discussion

Based on the results of the table, it can be affirmed that balneotherapy alleviates pain in patients suffering from low back pain, as all the essays found that there was an improve in the symptoms. However, more than a half of the studies (53,33%), did not find statistically evidence. It is difficult to extract statistically significant results from each study, and also comparing the studies between them. According to Morer et al. 2017; the current randomized clinical trials are very heterogeneous (23). Roques & Queneau, 2016; named three causes of that poor results: limited enrolment of patients, an insufficient duration of follow-up, and inhomogeneity of treatments (20).
Each study was made in different places, so the characteristics of mineral water were different too, according to the temperature and the mineralization. Furthermore, as this review shows at introduction, there are several categories of low back pain, so it is complicated to talk about it as a unique disease. Results can not be significant taking into account the heterogeneity between the essays. Well-designed studies are necessary to extract more acute information of the effect of mineral water in low back pain patients (20, 23, 26, 27). This study can not prove that balneotherapy is an effective treatment for low back pain, but it shows that it is necessary to continue investigating the effects of mineral water, and encourages researchers to carry out.

Table 1. Effectiveness of balneotherapy in low back pain.

Tittle	Authors	Year	Material and methods	Results
Dead Sea mud packs for chronic low back pain (18)	Abu-Shakra, M., Mayer, A., Friger, M., Harari, M.	2014	46 consecutive patients suffering from CLBP randomized into two groups: one group was treated with mineral-rich mud compresses, and the other with mineral-depleted compresses. Mud compresses were applied five times a week for 3 consecutive weeks.	Pain severity was reduced in patients treated with mineral-rich mud compresses compared with those treated with mineral-depleted compresses. Whether this modest effect is the result of a "true" mud effect or other causes can not be determined in this study
Effect of thermal water and adjunctive electrotherapy on chronic low back pain: a double-blind, randomized, follow-up study (19)	Kulisch, A., Bender, T., Németh, A., Szekeres, L.	2009	71 patients who underwent 20-minute daily treatment sessions with medicinal water or with tap water, both at a temperature of 34 degrees C, on 21 occasions. Both groups underwent additional adjunctive electrotherapy. The treatment was carried put during 15 weeks	In the group treated with thermal water, improvement occurred earlier, lasted longer and was statistically significant
[SPA therapy for pain of patients with chronic low back pain, knee osteo-arthritis and fibromyalgia] (20)	Roques, CF., Queneau, P.	2016	10 randomized controlled trials, 1192 patients	Pain was significantly improved by balneotherapy and significantly better improved than by control treatments. However several methodological biases were observed in many trials, mainly a lack of statistical power due to a limited enrolment of patients, an insufficient duration of follow-up, an inhomogeneity of treatments.
The effectiveness of balneotherapy in chronic low back pain (21)	Onat, ŞŞ., Taşoğlu, Ö., Güneri, FD., Özişler, Z., Safer, VB., Özgirgin, N.	2014	81 patients with LBP were followed up in two groups for a 3-week treatment program. Patients in group I (n = 44) were treated with physical therapy alone. Patients in group II (n = 37) were treated with balneotherapy in addition to the same physical therapy protocol in group I. Patients in both groups were given a home-based standardized exercise program	All of the measured parameters improved in both groups. However, improvements in pain, functionality, and quality of life scores were found to be superior in the balneotherapy plus physical therapy group. For the patients with CLBP, balneotherapy plus physical therapy is more effective, compared to physical therapy alone
The effects of the calcium-magnesium-bicarbonate content in thermal mineral water on chronic low back pain: a randomized, controlled follow-up study (22)	Gáti, T., Tefner, IK., Kovács, L., Hodosi, K., Bender, T.	2018	105 patients suffering from CLBP. The control group (n = 53) received the traditional musculoskeletal pain killer treatment, while the target group (n = 52) attended thermal mineral water treatment for 3 weeks for 15 occasions.	All of the investigated parameters improved significantly in the target group by the end of the treatment, and this improvement was persistent during the follow-up period There were no significant changes in the measured parameters in the control group. Based on the results, balneotherapy might have favorable impact on the clinical parameters and quality of life of patients suffering from CLBP

The role of mineral elements and other chemical compounds used in balneology: data from double-blind randomized clinical trials (23)	Morer, C., Roques, CF., Françon, A., Forestier, R., Maraver, F.	2017	27 double-blind randomized clinical trials. A total of 1118 patients with rheumatological and other musculoskeletal diseases were evaluated in these studies: 147 for CLBP. 82 of these participants were assigned to the experimental group. They were treated with mineral water baths and/or mud/peloid (with or without other forms of treatment, like physical therapy, exercise…). The rest were allocated to the control group; they received mainly tap water and/or "non-mineral" mud/peloid treatments.	Mineral water or mud treatments had better and longer improvements in pain, function, quality of life, clinical parameters, and others in some rheumatological diseases. Internal validity and other limitations of the study's methodology impede causal relation of spa therapy on these improvements. Existing research is not sufficiently strong to draw firm conclusions
Comparison of the effects of land-based and water-based therapeutic exercises on the range of motion and physical disability in patients with chronic low-back pain: single-blinded randomized study (24)	Nemcić, T., Budisin, V., Vrabec-Matković, D., Grazio, S.	2013	72 patients hospitalized for inpatient treatment in a special rehabilitation hospital, 36 patients performed a 3-week standardized program of group water-based exercises and the other 36 performed a program of group land-based exercises. All patients were also treated with electro analgesic therapy and underwater massage.	In the sample of patients with chronic low back pain, exercise treatment improved lumbar motion and decreased the level of physical disability. However, comparison of land-based exercises and water-based exercises in thermal mineral water did not demonstrate any significantly different result.
Evidence-based hydro- and balneotherapy in Hungary--a systematic review and meta-analysis (25)	Bender, T., Bálint, G., Prohászka, Z., Géher, P., Tefner, IK.	2014	Systematic review and meta-analysis of clinical trials. 122 studies identified in different databases include 18 clinical trials. 5 of these evaluated the effect of hydro- and balneotherapy on chronic low back pain	Balneotherapy with Hungarian thermal-mineral waters is an effective remedy for lower back pain
Aquatic exercise & balneotherapy in musculoskeletal conditions (26)	Verhagen, AP., Cardoso, JR., Bierma-Zeinstra, SM.	2012	A review of 30 years	Exercises in general, and specifically aquatic exercises, are beneficial for reducing pain and disability in many musculoskeletal conditions demonstrating small to moderate effect. Balneotherapy might be beneficial, but the evidence is yet insufficient to make a definitive statement about its use
Balneotherapy for chronic low back pain: a randomized, controlled study (27)	Kesiktas, N., Karakas, S., Gun, K., Gun, N., Murat, S., Uludag, M.	2012	60 patients with CLBP were randomly divided into two groups. Physical modalities plus exercise were applied to group 1, and group 2 was received balneotherapy plus exercise for 10 sessions	Balneotherapy combined with exercise therapy had advantages than therapy with physical modalities plus exercise in improving quality of life and flexibility of patients with CLBP

The effect of spa therapy in chronic low back pain: a randomized controlled, single-blind, follow-up study (28)	Tefner, IK., Németh, A., Lászlófi, A., Kis, T., Gyetvai, G., Bender, T.	2012	60 patients with CLBP pain were randomized into two groups. The treatment group received balneotherapy with thermal-mineral water, and the control group bathed in tap water	The study demonstrated the beneficial effect of balneotherapy with thermal mineral versus tap water on clinical parameters, along with improvements in quality of life
Additional therapeutic effect of balneotherapy in low back pain (29)	Dogan, M., Sahin, O., Elden, H., Hayta, E., Kaptanoglu, E.	2011	60 patients with lumbar spondylosis were included in the study. In Group 1, patients received both balneotherapy and physiotherapy and in Group 2, patients received only physiotherapy for 3 weeks	There was no statistically significant difference between the two groups. All clinical parameters significantly improved patients in both of the groups. The study reiterated that besides conventional physiotherapy, balneotherapy may be effective in the treatment of patients with CLBP
[Spa therapy in rheumatology. Indications based on the clinical guidelines of the French National Authority for health and the European League Against Rheumatism, and the results of 19 randomized clinical trials] (30)	Françon, A., Forestier, R.	2009	19 randomized controlled trials that comprised a statistical comparison of between-group outcomes	16 studies indicated a persistent improvement (at least 12 weeks) in pain, analgesic and non-steroidal antiinflammatory drug consumption, functional capacity and/or quality of life in CLBP. Spa therapy, or hot-water balneology, appears to be indicated for CLBP, stabilized rheumatoid arthritis, ankylosing spondylitis and fibromyalgia.
Effectiveness of aquatic exercise and balneotherapy: a summary of systematic reviews based on randomized controlled trials of water immersion therapies (31)	Kamioka, H., Tsutani, K., Okuizumi, H., Mutoh, Y., Ohta, M., Handa, S., Okada, S., Kitayuguchi, J., Kamada, M., Shiozawa, N., Honda, T.	2010	Systematic reviews based on randomized clinical trials that included at least 1 treatment group that received aquatic exercise or balneotherapy. Articles published from the year 1990 to August 17, 2008	Aquatic exercise had a small but statistically significant short-term effect on locomotor diseases. However, the long-term effectiveness of balneotherapy in curing disease or improving health remains unclear
The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials (32)	Falagas, ME., Zarkadoulia, E., Rafailidis, PI.	2009	3 randomized controlled trials, examining the clinical effect of balneotherapy in CLBP	The available data suggest that balneotherapy may be truly associated with improvement in several rheumatological diseases. However, existing research is not sufficiently strong to draw firm conclusions

5 Conclusions

1. Balneotherapy could be beneficial treating patients suffering from low back pain, but there is still not enough quality scientific evidence.
2. Well-designed studies are necessary to provide evidence to balneotherapy treatments.

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