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Tattooing-induced inflammatory reactions, unusual trigger factor for stroke in a young man chronic user of tobacco and marijuana, with unknown neurovascular anatomical variants and patent foramen ovale – a “happy ending” case report

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Abstract

Introduction: Extensive tattooing co-occurring with other lifestyle risk factors (cannabis and tobacco smoking) represents unhealthy behavior trends in some groups of teenagers and young adults.

Case report: This case study synthetically presents a 2 years evolution of a 37-year-old man, with 20-year history of progressive and regular cannabis exposure and tobacco smoking. In January 2017 he suffered a severe paramedian thalamo-mesencephalic embolic stroke of undetermined source and coma, preceded by laborious tattooing maneuvers. Uncommon anatomical variants of cerebral circulation (a right-sided fetal type posterior cerebral artery and an inferred artery of Percheron) were detected. The rehabilitation program and abstinence from smoking tobacco and marijuana led to significant neurologic improvement, with no vascular recurrence until September 2018, when he suddenly suffered from a transient ischemic attack in the vertebrobasilar arterial territory. Recurrence of the cerebral ischemic event during a disciplined program of abstinence imposed clinical re-examination, blood analysis, peripheral venous Doppler, 24-hours ECG Holter. Finally transesophageal echocardiography has revealed the embolic source, and detected patent foramen ovale (PFO) with minimal shunt. He was informed that he should undergo PFO closure. His first option was for conservatory management, using a dual antiplatelet medication (75 mg clopidogrelum, 75 mg aspirin). In October 2019 his cardiac congenital malformation was successfully operated. Case closed.

Discussion: Stroke was triggered by extensive tattooing maneuvers that induced bleeding, local and systemic inflammatory reactions, in a young person predisposed to cerebral infarction. The complex physiopathological picture included a "puzzle" of harmful xenobiotics (contained in cannabis and tobacco smoke, respectively in tattooing ink), overlapping with the unknown pre-existing asymptomatic cardiac malformation, and neurovascular uncommon anatomic variant. Prevention of stroke in young adults is the primary treatment strategy, as Hippocratic Oath postulates: "I will prevent disease whenever I can, for prevention is preferable to cure". Healthcare professionals must educate people and promote prophylactic interventions against modifiable risk factors. Secondary prevention of recurrent strokes must be directed towards etiology, and mechanisms responsible for the incident, and a rigorous management of additional risk factors.

Key words: tattooing; cannabis; tobacco; artery of Percheron; patent foramen ovale; stroke,

Introduction

Nowadays, extensive tattooing and body piercing co-occurring with cannabis, alcohol, and tobacco smoking represent increasingly common forms of self-expression and behavioral trends in some groups of teenagers and young adults. Tattooing is a very common practice, and the number of people getting tattooed has substantially increased in recent years, encompassing 24% of the population in certain countries (1,2). The presence of bigger tattoos could be a rough indicator of possible emotional problems, depression, neuroticism, aggressive and violent behavior, drug abuse, risky sexual behaviors and promiscuity, increased risk for hepatitis B and/or C, even traffic offences (3,4).

Complications from decorative tattoos are relatively rare but can be unpredictable (1,2,5,6).

Risks may be increased with the current trend of home-based tattooing, especially in unhygienic settings or with inappropriate conservation of inks.^{5,6} Marijuana is one of the most commonly used recreational drugs worldwide. Increasing evidence now links cannabis to the pathogenesis of cardio-cerebrovascular diseases in young adults, with a recorded 25.6% death rate associated with cannabis-related harm (7,8). In many EU countries, medical use of cannabinoids is authorised, but this should not become an argument for “unfettered and uncontrolled consumption” (9).

Romanian National Anti-Drug Agency estimated a 3.3% prevalence of regular cannabis use among young people aged between 15-34 years, with males comprising 4% and females, 2.7% (10).

Illicit cannabis (“weed, pot, grass, herb”) is much more “powerful” than it was 40-50 years ago. Tetrahydrocannabinol (THC) levels have steadily increased from less than 1% in the mid-1970s, to 3% in 1980, 6% in 2002, approximately 8.5% in 2008 (11), and 12 % in 2012 (12). Many cardiovascular effects reported in recent papers are related to the increased content of THC (100–250 mg/joint, compared to 10 mg/joint in the 1960s (13).

Marijuana is an interactive cardiovascular negative factor in addition to alcohol, tobacco, and opioids, being associated with increased risk for stroke/transient ischemic attack (TIA), atrial fibrillation, myocardial infarction, and lower limbs arteritis (14-18). It is a precipitating factor for cerebral vasospasm and stroke, especially in chronically addicted young adults (16).

Case report

The patient and his next of kin have given written consents (in 2017 and 2018) to the inclusion of material pertaining to the case.

This case study synthetically presents the evolution of a 37-year-old man since January 2017 to today's days. He had a 20-year history of progressive and regular cannabis exposure and tobacco smoking (30-40 cigarettes daily). A timeline follow-back measure revealed that he had started smoking 1-2 “joints” weekly when he was 17 and then progressively increased the doses, becoming a “heavy” consumer (5-6 “joints” daily) over the past 4-5 years. He denied using alcohol or other street drugs. He had multiple, extensive and elaborate tattoos on his neck, arms, thorax and abdomen (fig.1) mainly in black ink, purchased online from American websites. The artist used to keep the ink in non-sterile receptacles.



Fig.1 Elaborate extensive tattoos; a large unfinished one is on the left flank.

In January 2017 he suffered a severe paramedian thalamic-mesencephalic embolic stroke of undetermined source and coma, preceded by laborious tattooing-maneuvers. He was diagnosed with uncommon anatomical variants of cerebral circulation: a right-sided fetal-type posterior cerebral artery (FPCA) and an inferred artery of Percheron (AOP) (19).

Neurological events were triggered by a “kaleidoscopic” association: laborious and painful tattooing maneuvers (lasting about 4½ hours) using unverified ink, application of a local gel with anti-inflammatory and anesthetic properties, smoking four “joints”. A few hours later he complained of chills and subfebrility, dizziness, diplopia, slurred speech, disturbed balance, left third cranial nerve palsy (palpebral ptosis, divergent strabismus with unilateral mydriasis), right ataxic hemiparesis, and fluctuating consciousness. He dramatically deteriorated to coma (GCS 7/15) due to a paramedian thalamic and midbrain infarction. An evolutionary sequence of his medical history was presented in a previous article focused on anatomical, imagistic and pathophysiological aspects.

Sustained rehabilitation and abstinence from tobacco and cannabis led to favorable outcomes: modified Rankin score was 2 at four months after discharge, respectively 1, after twelve months. The patient was carefully followed-up, and had a favorable outcome with no vascular recurrence for 20 months. Imagery reflected the good clinical evolution (fig.2 and 3)

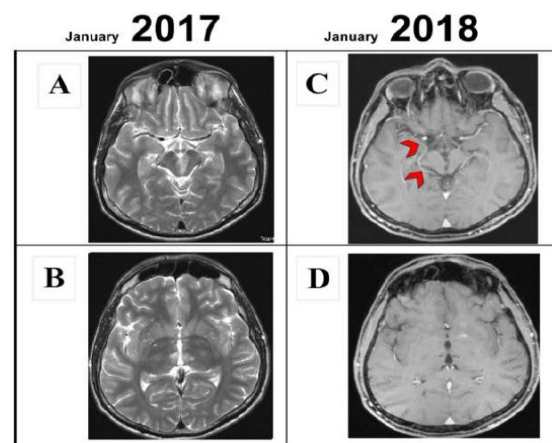


Fig. 2 MRI aspects recorded in January 2017 (A, B), and January 2018 (C, D).

(A, B): Axial T2-weighted brain images at mesencephalon and thalamus levels. Paramedian thalamic and rostral midbrain hyperintense aspects were suggestive for acute Percheron's artery infarction.

(C, D): Axial T1-vibe sequences. Red arrows point the fetal-type posterior cerebral artery (FPCA). Multiple lacunae in the midbrain and paramedian thalamic nuclei are present.

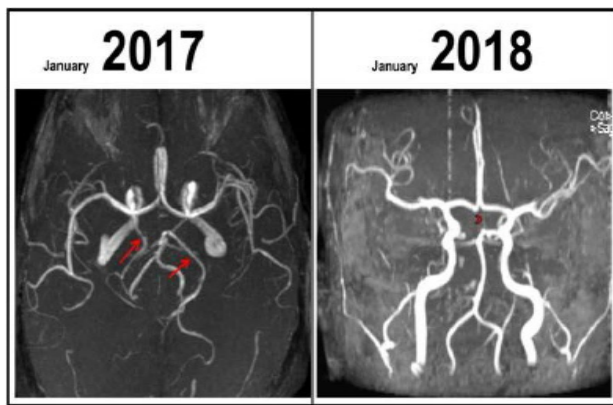


Fig. 3 Magnetic resonance angiography (MRA) recorded in January 2017. Posterior cerebral arteries are indicated by red arrows. Right fetal origin of the posterior cerebral artery (FPCA), arising directly from the internal carotid artery. Left thalamoperforating arterial group was not visualized, AOP was inferred. MRA control in January 2018 revealed permeabilization of one arteriole in the group of the left thalamoperforating arteries (arrow head).

In September 2018, during a disciplined abstinence program from tobacco and marijuana, he suddenly suffered from a transient ischemic attack (TIA) in the vertebrobasilar arterial territory (dizziness, nausea, axial ataxia), lasting about 15-20 minutes, possibly precipitated by morning hypoglycemia.

Clinical examination, peripheral venous Doppler, 24-hours ECG Holter monitoring did not reveal any embolic source. Repeated blood tests (white blood cells count, hemoglobin, electrolytes, cholesterol and triglycerides, liver and renal function) revealed normal results.

Repeated clotting tests were normal (antithrombin III was 98% (>80%), homocysteine was 8 mol (≤ 12), lupus anticoagulant was negative, antinuclear antibodies were 0.2 UM (<0.7), C reactive protein was 110% (70-130%).

Cerebral CT scan showed old lacunar images, and no additional abnormalities, no evidence of cerebral hemorrhage or encephalitis (fig.4).



Fig. 4 Axial CT scan performed in September 2018. Lacunar lesion in the midbrain.

Transesophageal echocardiography revealed a small patent foramen ovale (PFO, with no hemodynamically significant systolic shunt), which has not been disclosed in 2017 by transthoracic echography. No explanation for recurrent TIA other than PFO was found.

Confronted to a cryptogenic embolic ischemic stroke found to have PFO, with a risk of paradoxical embolism (RoPE score 6, with a 62% chance of PFO-related causality, and 8% risk of 2 year recurrence of stroke/TIA) (20), the subject was guided to interventional cardiology. He was informed that he should undergo PFO closure; the risks and complications after the interventional manoeuvre were explained.

His first option was for conservatory management, using a dual antiplatelet medication (75 mg clopidogrelum and 75 mg aspirin), to prevent recurrent stroke and/ or TIA.

In November 2018 he submitted an aesthetic ophthalmologic intervention, for the residual left-eye oculomotor paresis. Neurological examinations (pre- and postophthalmologic surgery) have revealed neither disturbed balance nor coordination, motor or sensory deficits.

In October 2019 he was convinced to submit a successful PFO closure intervention.

He has been abstinent from tobacco and cannabis since his first cerebral event (2017) and maintained good adherence to the rehabilitation program until nowadays.

Discussion

This paper is a pretext to analyze the challenging physiopathological circumstances of a cryptogenic stroke and coma, “triggered” by unedited factors (local and systemic inflammatory reactions, resulting from prolonged and extensive tattooing maneuvers), in contextual relationship with a complex “puzzle” of harmful xenobiotics (found in cannabis, tobacco and tattooing ink), in a young man, chronic cannabis abuser and heavy smoker, with a peculiar cardio-cerebrovascular background: association of Percheron’s artery (only 140 cases described since 1973) with a foetal variant of cerebral posterior artery (only 4 cases with this association type have been described in literature), and a pre-existing asymptomatic cardiac malformation (patent foramen ovale).

The presentation is useful for the young healthcare professionals (GPs, cardiologists, neurologists, toxicologists) who should educate people and

promote prophylactic interventions against modifiable risk factors for stroke in young adults, because prevention is the primary treatment strategy. Chronic intoxication with a “puzzle” of harmful xenobiotics may be incriminated in stroke pathogenesis, in predisposed individuals.

The initial diagnostic approach (19) had some important etiological weakness, because contrast transcranial Doppler ultrasound in the detection of right-to-left shunts, mobile cardiac telemetry and transesophageal echocardiography were not available. All were recommended as future investigations and mandatory for an analytical diagnostic procedure.

Recurrence of the cerebral ischemic event during a disciplined program of abstinence from tobacco and marijuana, without an apparent embolic source imposed investigations who revealed the cardiac congenital malformation, predisposing factor to paradoxical embolism.

The patient had neither atrial septal aneurysm, nor large PFO, cardiac or valvular pathology. No other peripheral sources of embolism were found, and TIA was less likely to have been caused by the common vascular risk factors.

The peculiarity of the case consists in the distinct pathophysiological context, associating a chronic unhealthy lifestyle with two asymptomatic predisposing conditions: the patent foramen ovale (PFO) and the unusual pre-existing neurovascular background (19).

Laborious tattooing maneuvers have generated multiple hypodermic trauma, bleeding, inflammation (rash), micro-clots (possibly source of paradoxical embolism), systemic inflammatory reaction (fever and chills), preceding the cerebral infarction.

Before tattooing he applied a local gel with anti-inflammatory and anesthetic properties. Each gram contains 5 mg piroxicam, 5 mg cyclobenzaprine hydrochloride (tricyclic analgesic with local anti-serotonin action), and 20 mg lidocaine. The producer's recommendations are 0.5-1 g of gel over an area 3-4 cm in diameter, corresponding to 7-12 cm². Anamnesis revealed an overdose of gel, applied on approximately 300 cm² of skin.

Tattoo ink can contain numerous potentially allergenic or carcinogenic ingredients, bacteria, viruses, and fungal species (21,22). It is a complex medium composed of solvents, pigments (azo dyes and metallic salts), resins, lubricants, surfactants, fluorescents, additives that confer color and fluidity, as well as hazardous chemicals, such as polycyclic

aromatic hydrocarbons (43%), primary aromatic amines (14%), heavy metals (9%), preservatives (6%) and possible microbiological contamination (11%) (23). There are neither standards issued nor established methods for a quantitative determination of chemicals in tattoo and permanent make-up inks, that often have unknown or highly variable composition (24,25). Production of tattoo ink and pigments is unregulated in the USA (24), and no coloring agent has been officially approved by the FDA for injection under the skin (25). The safety of tattoo inks is somewhat higher in Europe, because of the improved quality control of pigment raw materials (22,23).

The most common complication of a decorative tattoo is a transient local acute inflammatory reaction, due to multiple needle punctures (26-29). Fujita et al (1988) demonstrated that Indian ink particles and latex beads were endocytosed by fibroblasts and macrophages in the dermis and subcutis (26). Deposition of exogenous pigments into the skin may induce immune-mediated reactions, hypersensitivity or allergy to tattoo pigments, may generate haptens in the skin (26-28), and even vasculitis (29). Repetitive traumatic punctures of the skin create conditions for bleeding, blood absorption of the ink, and implicit activates the coagulation cascade.

Vascular injury is associated with increased expression of adhesion molecules by the endothelial cells, recruitment of inflammatory cells, synthesis of proinflammatory cytokines (tumour necrosis factors, interleukins, lymphokines, monokines, interferons) and proteases, with negative repercussions on the endothelium, vascular smooth muscle cells and the extracellular matrix (30). Cytokines can influence the mitochondrial redox system, increasing the production of reactive oxygen species (31). Clinical and experimental evidence implies inflammation in the physiopathology of stroke. Systemic circulating inflammatory molecules and immune cells are capable of activating microglia, inducing cerebral neuroinflammatory response and contributing to ischaemic events (32-34). Positron emission tomography imaging has demonstrated activated microglia, involving a “primed” inflammatory environment in the brains of subjects associated with multiple risk factors(34).

Ink and topical analgesic substances (lidocaine, cyclobenzaprine and piroxicam) may have been interacting with the remaining phytocannabinoids in the tissues.

THC and its main active metabolite, 11-hydroxy-delta 9-THC, as well as other phytocannabinoids are highly lipophilic, cross the blood-brain barrier, and are stored in the liver, lung, spleen, and neutral fat cells, including in the hypodermis. Its half-life is approximately eight days and complete elimination of a single dose in humans can take up to one month (13,14,35).

In addition to 100 phytocannabinoids identified in the plant (14), street cannabis contains additives such as solvents, industrial etchants, pesticide derivatives, and chemical sugars intended to amplify the psychotropic effects. These substances may also have concomitant cardiac side effects (13).

Cannabis abusers in the general community are usually young people, and have a higher rate of non-fatal strokes or transient ischemic attacks compared with non-cannabis users (15,36). A heavy marijuana users' lifestyle is associated with consumption of tobacco (34%) and/or alcohol (11%) (17,36,37). The subject reported at least two behavioral risk factors: cannabis abuse and tobacco intoxication (defined by a daily cigarette consumption of more than 20 pieces, according to Fagerström nicotine dependence scale) (38).

Tobacco and cannabis combustion products represent well-documented cardio-cerebrovascular risk factors and can induce chronic cellular intoxication. One minute of marijuana secondhand smoke exposure (passive inhalation) substantially impairs vascular endothelial function, to a comparable extent as exposure to tobacco smoke inhalation, but recovery is considerably slower for marijuana (39).

One might assume that during the last two decades the subject was systematically exposed to over 4,000 toxic products of tobacco combustion, including at least 70 known carcinogens such as hydrogen cyanide, tar, formaldehyde, acetaldehyde, lead, arsenic, ammonia, nitrosamines, benzene, other polycyclic aromatic hydrocarbons, nicotine, and carbon monoxide (40), resulting in a chronic cellular intoxication. Heavy marijuana consumption amplifies the vulnerability to ischemic stroke, by increasing oxidative stress and cerebral mitochondrial respiratory chain dysfunction (41).

Cryptogenic stroke accounts for 30% to 40% of ischemic stroke (42,43). A literature search found one case report of cardioembolic stroke in Percheron's vascular territory in a young man with patent foramen ovale, who smoked cannabis on a daily basis and used ketamine on occasion (44).

The diagnostic workup is essential to determine the possible mechanisms involved in the pathogenesis of cryptogenic stroke: occult paroxysmal atrial fibrillation, PFO, aortic arch atherosclerosis, atrial cardiopathy. PFO was found in 40% of patients with cryptogenic stroke and may be associated with paradoxical emboli to the brain (45,46).

With the advent of transesophageal echocardiography and transcranial Doppler, PFO can be routinely detected in clinical practice (43,46). The reported case had a recurrent cryptogenic ischemic cerebral event (TIA) who was attributed to PFO, detected with transesophageal echocardiography. The patient had neither an atrial septal aneurysm, nor a large interatrial shunt (47), and the stroke was less likely to have been caused by the common vascular factors, cardiac or valvular pathology.

No explanation for the recurrent TIA other than PFO was found on repeated investigations. The diagnostic workup limitation has persisted, due to the absence of prolonged, repeated ECG monitoring, to detect occult atrial fibrillation (47,48).

Management of cryptogenic stroke in young adults with PFO remains subject to controversy. Therapeutic management for secondary stroke prevention in patients associating PFO and cryptogenic stroke include medical treatment with antiplatelet agents or anticoagulants, respectively surgical closure or percutaneous device (45-52).

A quite recent meta-analysis of PFO closure trials has suggested potential, but uncertain benefit of PFO closure over medical management (49). Other systematic reviews and meta-analysis regarding percutaneous closure versus medical therapy for stroke with PFO emphasized that rates of recurrent stroke were significantly lower with PFO closure than with medical therapy alone (47,48, 50-52). Closure reduced the incidences of stroke recurrence in patients with cryptogenic events, and the composite outcome of cerebral infarction, TIA, or all-cause death, but increased risks for atrial fibrillation or atrial flutter and pulmonary embolism compared with medical therapy (51,52). The rate of new-onset atrial fibrillation or flutter was higher in the PFO closure group patients (4.6% vs. 0.9 %) (47,51). The subject was informed that he should undergo PFO closure; the risks and complications after the interventional maneuver were explained. His first option was for conservatory management, using dual antiplatelet medication (clopidogrelum 75 mg and aspirin 75 mg).

Finally he was convinced to submit a successful PFO closure intervention (in October 2019).

The case reported is illustrative for the medical staff's obstinacy to reveal the cryptogenic underlying pathology, and also for the patient's ambition, hard work and compliance.

The subject didn't know that for decades he had "*Damocles' sword*" above his head, and adopted a hazardous lifestyle, playing "*Russian roulette*" with his *destiny*.

After the neurologic event he changed to a totally different person. One must emphasize his discipline and consistency, with absolute abstinence from tobacco and cannabis smoking, essential factors for his favorable neurologic evolution and excellent outcome.

Prevention of stroke in young adults is the primary treatment strategy, as Hippocratic Oath postulates: "***I will prevent disease whenever I can, as prevention is preferable to cure***".

Healthcare professionals should educate people and promote prophylactic interventions against modifiable risk factors. The general practitioner occupies an essential position in the approach of prophylactic health education.

Secondary prevention of recurrent strokes must be directed towards stroke etiology, the mechanisms responsible for the incident, and the rigorous management of additional risk factors (42,53).

Systematically medical education is essential for both primary and secondary prevention.

List of Abbreviations

AOP, artery of Percheron
CT, computed tomography
ECG, electrocardiography
FPCA, fetal posterior cerebral artery
GCS, Glasgow coma scale
MRA, magnetic resonance angiography
MRI, magnetic resonance imaging
PCA, posterior cerebral artery
PFO, Patent foramen ovale
RoPE (score), risk of paradoxical embolism
THC, tetrahydrocannabinol
TIA, transient ischemic attack

Compliance with Ethical Standards The authors disclose any potential conflicts of interest.

Written informed consent has been obtained from the patient's next of kin (wife 2017), then from the patient (2018), for the inclusion of material pertaining to the case. Institutional consent for publication was obtained from our Hospital Ethic Commission.

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The impact of cognitive decline on stroke rehabilitation

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Abstract

Introduction. Stroke is a disease of great public importance, the second leading cause of death and the third leading cause of disability. The persistent and progressive decline of cognitive function in stroke survivors has a major impact on the patient's health and quality of life, with repercussions affecting the whole society. There is no cure for cognitive impairment or dementia, apart from the non-pharmacological treatment meaning the rehabilitation, which may be an important effective alternative.

Material and method. We performed a retrospective study for a period of 6 months. The patient population consisted of 60 individuals. Their primary diagnosis was stroke and the secondary was dementia. Patient assessment was done by clinical, imagistic and psychiatric examination. In addition, an analysis of randomized controlled data trials from the literature, on cognitive rehabilitation had been performed.

Results and discussions. The results show that 83,33% of patients were diagnosed with mixed dementia but 60% had this diagnosis before brain damage occurred, with a Mini Mental State Examination under 20 points. The most common disorders of cognition were: fixation hypomnesia, temporal-spatial disorientation, impaired computing. Dementia patients have different rehabilitation needs and associate a lower functional result than those without cognitive impairments. For a rehabilitation benefit, patients should be able to recover their skills step by step and carry them over to the next session, which is difficult for people with severe memory problems. They have a low potential for progress and require a long time and many resources to advance with neurorehabilitation.

Conclusions. The brain injury, such as stroke, causes damage of motor and cognitive functions with repercussion on quality of life. The cognitive decline associated with stroke is an important aspect of neurorehabilitation. Nevertheless is slightly neglected to the detriment of physical disability as there is a lack of recovery potential in these patients.

Key words: *dementia, stroke, cognitive, neurorehabilitation,*

Introduction

Worldwide, cerebrovascular accidents are the second leading cause of death and the third leading cause of disability (1).

In 2017, the Stroke Alliance for Europe (SAFE) with the European Stroke Organisation (ESO), launched a comprehensive overview of stroke in Europe and they showed that between 2015 and 2035 the number of strokes is expected to rise by 34% due to an ageing population (2).

The life expectancy of patients with stroke has increased due to the fast application of an advanced treatment, but the aging population increases the incidence of cognitive decline. Also, the sudden death of brain cells due to lack of oxygen when the blood flow to the brain is lost by blockage or rupture of an artery, is a major cause of dementia (3). Thus,

the two entities are associated quite frequently, especially in the over-60 age group.

Current evidence suggests that 25-30% of stroke survivors develop immediate or delayed vascular cognitive disorders leading to dementia (4). Therewith 10% of patients have a diagnosis of dementia prior to first stroke, one third of patients develop dementia after recurrent stroke and many others may have undiagnosed pre-stroke cognitive impairment (5).

Patients with stroke who have cognitive impairments in addition to physical impairments have less recovery of physical function, more dependence in living after stroke (6), growth risk of mortality lower the quality of life.

Material and method

We performed a six-month retrospective study in the Department of Neurology at the Emergency County Hospital "St. Apostol Andrei" Galati, in which we included 60 patients with main diagnosis of stroke, and secondary diagnosis of dementia. We have analyzed correlation between computer tomography images corresponding to brain damage and the severity of cognitive decline associated measured with Mini Mental State Examination (MMSE).

Results and discussions

During 6 months, a number (n) of 463 patients suffered a stroke and 60 patients had secondary diagnosis of vascular, mixed dementia or Alzheimer's disease. We included in our study only the patients who associated stroke and dementia.

We would like to draw the attention to the two terms: post stroke dementia (PSD) and vascular dementia (VD). Post-stroke dementia involves both neurodegenerative and vascular processes, that means a mixed dementia, while vascular dementia develops after a vascular event that can be highlighted on the neuroimaging, computer tomography (CT) or magnetic resonance imaging (MRI). VD represents a concept which includes not only multiple cortical and/or subcortical infarcts, but also strategic single infarcts, non-infarction white matter lesions, hemorrhages, and hypoperfusion as possible causes of dementia (7).

In order to be able to make a proper classification, we must know the cognitive state before the injury. We found that 83,33% (50 patients) were diagnosed with mixed vascular dementia, 11,67% (7 patients) with vascular dementia and 5% (3 patients) with Alzheimer's disease.

Stroke can facilitate the onset of vascular dementia as well as aggravate pre-existing cognitive decline that manifest immediately, within three months of the event. In contrast, there are cases that develop dementia delayed or only after recurrent stroke. This delay can be seen as a therapeutic time window allowing interventions to be applied to preserve cognition following stroke (8).

During the study, 53,33% of patients (n=32) had a diagnosis of dementia before the onset of brain injury, and 41,66% of patients (n=25) had recurrent cerebral infarctions. It is a fairly high percentage of recurrent vascular accidents, which argues that neurodegeneration predisposes to new brain damage. Recurrent stroke can be prevented by drug intervention, but post-stroke dementia can't be

slowed down with any medication. It can be tried with a secondary prevention that involves modifiable risk factors like: healthy diet, regular exercise, reduce the chronic stress, social interaction. Pre-existing dementia is associated with higher levels of disability and risk of death (9). They have a bigger probability to be institutionalized after stroke comparing to patients without pre-existing dementia (9).

A study comparing short-term outcomes for 919 stroke patients found that whilst the 11.5% of patients with pre-existing dementia had a higher level of disability at baseline and discharge than patients without (10). They made similar daily gains in motor function as measured using the Functional Independence Measure (FIM), a validated tool within stroke rehabilitation (10).

Skills such as: abstract thinking, judgment, short-term verbal memory, understanding and guidance are important to predict the functional status of the stroke survivor.

Regarding the stroke type, patients with ischemic strokes usually have higher survival rates than those with hemorrhagic strokes, which explains why ischemic strokes lead to psychiatric morbidity more frequently than do hemorrhagic strokes (11).

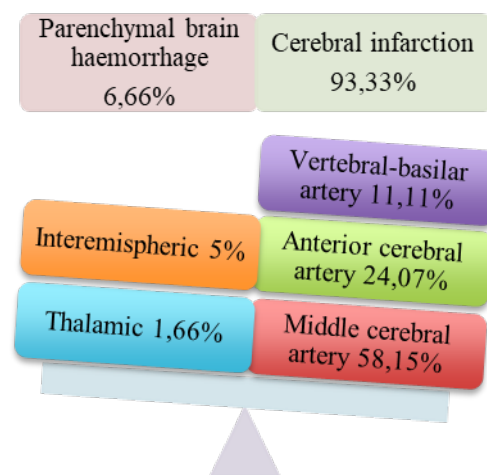


Fig 1. Stroke diagnosis upon discharge

In our study parenchymal brain hemorrhage had 6,66% (n=4) of patients, 3 patients with interhemispheric and 1 patient with thalamic hemorrhage. Cerebral infarction had 93,33% patients (n=56), anterior cerebral artery was involved in 24,07% cases (n=13) and the middle cerebral artery in 58,15% cases (n=37), with 56,75% (n=21) on the right side and 43,25% (n=16) on the left side.

In a right hemisphere middle cerebral infarct, visual-spatial perceptual disorders include left-sided neglect, figure ground disorientation, constructional

apraxia and astereognosis (12).

Thus patients with unilateral neglect syndrome, ignore the left side of the body, are disorientated, do not respond to sensory stimuli related to the affected part, they forget to use their hand when they dressed, when they eat. At the same time, these patients may associate anosognosia. They can get injured because they are not aware of the existing deficit on the affected side. Hier et al. found that after right hemispheric lesions, recovery from unilateral neglect and anosognosia was the most rapid (13).

Patients who had lesion in the middle cerebral artery on the left hemisphere, presented expressive, motor or mixed aphasia in 33,33% of cases (n = 20) and 15% of cases (n=9) presented apraxia. The disorder of the voluntary movement and the problems with understanding of language constitute a series of obstacles in carrying out the recovery plan.

Vascular brain injury and the resulting cellular damage (oxidative stress, swelling) appear to be the causes of the altered brain ageing process, leading to increased risk for stroke, cognitive decline, dementia, depression, and other neurological problems, such as gait disorders (14).

The prevalence of post-stroke cognitive decline has a broad range, from 20 % to 80 % (11). This variability depends on the diagnostic tools and the criteria employed, on the extent of the vascular and neurodegenerative pathologies before the stroke, on the cognitive status, on the stroke extension (volume) and topography (strategic areas such as frontal cortex, hippocampus or white matter) (15).

Dementia imaging provides important information about the anatomical substrate of the condition and can assess the degree of cognitive decline.

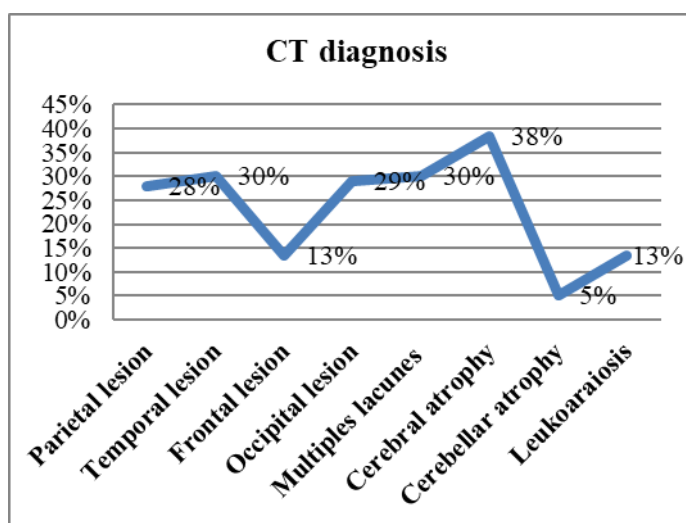


Fig 2. Different cerebrovascular pathologies associated with dementia- CT diagnosis

In figure 2 it is noticed that 30% of patients (n=17) had temporal lesion and in 6 cases was affected the dominant medial temporal lobe, that means this patients developed immediate cognitive syndrome.

Strategic infarct dementia is attributed to locations in the angular gyrus, the medial frontal lobe, and the inferomedial portion of the temporal lobe (16).

Frontal lesion was observed in 13,33% of cases (n=8) with repercussion on the executive function manifested by reducing the abilities: to control their impulses, to organize their thoughts, to change their priorities, to evaluate their progress. The functions normally associated with the frontal lobe are intellect, emotions, behaviour, language, personality, control centers for higher autonomic functions, abstract thinking and motor movement (7). The patients became emotional, impatient, rigid, with difficulties in concentrating and following the instructions given by the therapists. All of this can influence but also can predict the potential of the functional recovery.

A study of 663 occupational therapists working in stroke services in Canada found that when treating post-stroke cognitive impairment most therapists did not address executive function, which is often affected by vascular dementia (17).

Even more, there are exclusions to rehabilitation services in every international clinical guidelines. For example, in Spanish guidelines, rehabilitation is not recommended for patients with severe stroke and poor recovery prognosis (18). In Canada, patients must demonstrate the potential ability to return to pre-stroke levels of function or to increase post-stroke functional level (19). Given these issues, the patient with stroke and severe cognitive decline can't be a candidate for rehabilitation, but we believe that any minor gain that can improve their functional independence is a success in terms of growth the quality of life. Rehabilitation potential is difficult to predict due to the fact that some patients demonstrate their potential later than others (20).

Patients included in our study, with severe cognitive impairment, associated multiple CT images: 30% (n=18) silent lacunar infarctions, 38,33% (n=23) cerebral atrophy predominantly in the hippocampus, 13,33 % (n=8) lesions of the periventricular white matter.

The presence of silent multiple lacunar infarctions in patients with first-ever lacunar stroke is an independent predictor of poor performance on executive functions and short delayed verbal

memory tests (7). According to study of Grau-Olivares and Arboix ischemic cerebral small-vessel disease (SVD) should be regarded as a severe condition prodrome of subcortical VD, rather than a relatively benign disorder (21).

Bilateral hippocampal or thalamic infarctions and unilateral thalamic infarctions are other examples of strategically localized infarctions that are reported to cause dementia (22). In the hippocampal lesions the anterograde memory predominated. The patients were not able to accumulate new information, to store the recent experiences, to remember the natural course of the sequence of the tasks, all of these are necessary for the rehabilitation process. When thalamus lesions were also associated, patients suffered from retrograde amnesia. They can't remember their name, the familiar faces, the home.

A systematic review of the prevalence of memory impairment after stroke estimated that between 23% and 55% have memory impairment three months after stroke and between 11% and 31% a year after stroke (23). Cumming et al. notes that at one year post stroke, a majority of patients still had attention deficits, while deficits in language and memory were more likely to have resolved (24).

The most commonly used assessments for cognitive impairment or dementia after stroke are MMSE and Montreal Cognitive Assessment (MoCA). The MMSE evaluates especially dementia and we used it in our study: 40% of patients (n=24) had an MMSE score below 9 points, indicating a severe impairment of cognitive functions. Stroke patients with low scores are at high risk of dementia over time, even in the absence of recurrent stroke and should therefore be closely monitored for further cognitive decline.

Even minor stroke affects daily functioning, executive functions, and cognition, consequently affecting quality of life and return to work (7).

In the presented study, following the psychological examination the most common disorders of cognition were: fixation and evocation hypomnesia, temporal-spatial disorientation, disorders of mental calculation. It is difficult to work with these patients who are not aware of time or orientation in space. They can become anxious if they do not understand where they are or their purpose in that place.

In addition, cognitively impaired patients may not be able to benefit fully from rehabilitation because of their impairment. Research suggests that this may occur in patients with a sensory deficit (contralateral visual-neglect), attentional deficits or impaired comprehension and learning (6).

Conclusion

Brain injury through the infarction or cerebral hemorrhage, produces deficits consequences in motor and cognitive functions with repercussions on the rehabilitation plan. These patients have a low potential for progress, a reduced functional outcome implying different recovery needs and an individualized program, properly adapted to his deficits. They should be able to recover their skills step by step and carry them over to the next session, which is difficult for people with severe dementia.

Patients with severe cognitive impairment, objectively identified by a 9-point MMSE score, have associated multiple lacunar infarction, cerebral atrophy, periventricular white substrate lesions, and infarcts located strategically in the temporal or frontal lobe. It means that the severe dementia associates neurodegenerative process and vascular lesion.

The executive function, frequently affected in vascular dementia, recovered much harder than the motor one and has more psychosocial consequences causing permanent disability.

The cognitive decline associated with stroke is an important aspect of neurorehabilitation slightly neglected to the detriment of physical disability.

We need researches on the therapeutic plan of recovery of patients with stroke and dementia in order to increase their functional outcome and their level of independence.

There are no specific guidelines or recommendations regarding rehabilitation for these patients.

Author contributions.

The authors contributed equally to the work.

Declaration of conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Informed consent

Informed consent was obtained from all patients included in this study.

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Investigation the effect of oral Aloe Vera gel pills supplementation on the intensity of primary menstrual pain (Dysmenorrhea)

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Abstract

Introduction. This study was conducted to evaluate the effects of oral aloe vera gel pills supplementation on the intensity of menstrual pain. A randomized, single-blind clinical experimental plan was conducted amongst 150 single students aged 20 to 26 years who suffered from menstrual pain, at the Islamic Azad University of Medical Sciences from December 24, 2015 to October 22, 2016. The extent of pain was evaluated using the Cox Menstrual Symptom Scale (CMSC).

Material and method. Each participant was randomly assigned to aloe vera gel pill or the anti-PG drug Ibuprofen, ending with 60 participants in each group equally. The first trial group received 10 mg of aloe vera gel orally four times daily until the pain grade reached one or less. The control group received Ibuprofen and three tablets orally three times a day. The participants were permitted to take another drug that they usually took for their pain relief, in addition to the allocated treatment in case of continued pain. At the end of the trial, these participants were excluded in data analysis.

Results and discussions. Changes in the grade and the duration of the pain of participants were compared at the first and second months in both groups. Sample size was computed using $\alpha = 5\%$ and absolute error equal to 0.24 for correlation between medication and pain with acceptable absolute precision formula (AAPF). Result of this study showed that the mean age was 22.1 ± 1.4 and 20.4 ± 1.2 years in aloe vera gel pills and Ibuprofen groups, respectively. No significant difference was observed for the matched characteristics studied between the treated groups. the mean pain grade amongst aloe vera group was decreased from 2.81 ± 0.65 to 2.02 ± 0.34 , while in Ibuprofen group from 2.48 ± 0.4 to 1.32 ± 0.15 , respectively, using the described given dose. As result obtained that there was no statistically significant decrease in pain duration for the women who received Ibuprofen compared to those who used aloe vera. Also there was no significant difference in pain grade between the groups at the second month of intervention ($p=0.61$). Pain duration at the second month of trial was similar between the both groups ($p=0.76$).

Conclusions. In conclusion we could suggest that aloe vera gel pill as a novel herbal pain killer represents an effective treatment for the menstrual pain with no important side effects, although further clinical trials are recommended to look at the possible side effects in an extended spectrum of subjects.

Key words: *Aloe vera gel, Dysmenorrhea, Menstrual pain, Medicine, Symptoms, Women,*

Introduction

Primary dysmenorrhea "Painful Periods" is a very common problem in young women. It is usually defined as cramping pain in the lower abdomen occurring at the onset of menstruation in the absence of any identifiable pelvic disease. A pain which is of uterine origin and directly linked to menstruation but with no visible pelvic pathology is called primary dysmenorrhea. and is distinguished from secondary dysmenorrhea, which refers to painful menses resulting from pelvic pathology such as

endometriosis. It usually presents during adolescence, within three years of menarche. It is unusual for symptoms to start within the first six months after menarche. Affected women and young girls experience sharp, intermittent spasms of pain, usually centered in the suprapubic area. Pain may radiate to the back of the legs or the lower back. Additionally, systemic symptoms of nausea, vomiting, diarrhea, fatigue, fever, headache or lightheadedness are fairly common.

Pain usually develops within hours of the start of menstruation and peaks as the flow becomes heaviest during the first day or two of the cycle. Population surveys suggest a wide variation in prevalence rate of dysmenorrhea from studies around the world including Iran reporting a range between 35% and 75%. To regulate uterine contractions and uterine tone, many effective drugs and regimens are described before and various studies have also been conducted, but a proper statistical analysis and interpretation are not available. Use of natural substances with therapeutic properties is not new but it has been used since ancient times. Nowadays, a number of drugs prescribed originate from plants and some natural precursors (19). Herbal and dietary therapies are especially suitable for treatment of disorders such as dysmenorrhoea, as they can be self-administered and are often easily available from pharmacies. A recent review of some trials evaluating the efficacy of herbal and dietary therapies in primary and secondary dysmenorrhoea showed that vitamin B1 taken daily may be an effective treatment for dysmenorrhoea. Sun et al., (2009) showed that the obtained pain scores after the treatment and few months of post-treatment in herbal group were significantly lower than those in the control group in women exposed to the dysmenorrhoea. Aloe Vera is a plant that belongs to Liliaceae family that grows easily in hot and arid regions (21). The existing mucilage tissue at the center of leaves in this plant that is also so-called aloe gel is used for various cosmetics and medical applications. The peripheral leaf cells in this plant produce bitter and yellow color latex that is called aloes. It is composed of anthracene hydroxyl derivatives including aloins A and B2 and derivatives such as A, B2, and C aloe resins. The other compounds are sugars such as glucose, mannose, and cellulose (18). It has various vitamins consisting of B1, B2, B6, C, E, and folic acid, and minerals such as calcium, sodium, magnesium, zinc, copper, and chrome. Aloe vera is an herbal plant used in a variety of medical conditions such as wounds healing and decrease tissue damages and the ancient Egyptians used Aloe vera for treatment of wounds, burnings, and infections for the first time. Additionally, the other nationalities had used this herbal by various techniques for several purposes. Some researchers demonstrated that aloe vera is one of the effective

cures for dysmenorrhea as it treats the menstrual cramps substantially. Some researchers showed that the Indian aloe is a stimulant of the uterus. Hence it is given in cases of painful menstruation. It possesses compound known as aloes which effectively promotes the sterility and treats disturbed menstrual activity and pain in women. Due to the possible side effects of synthetic drugs, there are many attempts for alternatives traditional or herbal treatments. Many evidences have reported that nutrition and metabolism may play an important role in the cause and treatment of menstrual disorders. Keeping this in view, this study was carried out to investigate the effect of different level of oral Aloe Vera gel supplementation on the intensity of primary dysmenorrhea in young women and teenage girls who studied in the Islamic Azad University of Medical Sciences, Iran.

Materials and Methods

Study Procedures

A randomized, single-blind clinical experimental plan was conducted amongst 150 single students aged 20 to 26 years who suffered from menstrual pain, at the Islamic Azad University of Medical Sciences from December 24, 2015 to October 22, 2016. Participants who were single, suffered from menstrual pain, accommodated at the campus of University of Medical Sciences and had no pathological disorders were included in this study. The eligible participants fulfilled the self-completed questionnaire and the scale form and were visited physically by a licensed gynecologist before randomization.

Experimental design

The extent of pain was evaluated using the Cox Menstrual Symptom Scale¹. Each participant was randomly assigned to aloe vera gel pill or the anti-PG drug Ibuprofen, ending with 60 participants in each group equally. The first trial group received 10 mg of aloe vera gel orally four times daily until the pain grade reached one or less. The control group received Ibuprofen and three tablets orally three times a day. The participants were permitted to take another drug that they usually took for their pain relief, in addition to the allocated treatment in case of continued pain. However, at the end of the trial,

¹ -(having no pain ≤ 0 , for ≥ 0.5 h ≤ 1 , for $0.5 - 1$ h ≤ 2 , for several hours ≤ 3 and several days ≤ 4).

these participants were excluded in data analysis. Changes in the grade and the duration of the pain of participants were compared at the first and second months in both groups. A two sectioned questionnaire was used to collect the data. The first section included the demographic data, menstrual history, smoking, diet, exercise and past medical and reproductive history that was completed before the intervention of the trial. The second section was designed to cover the grade and duration of pain and the accompanying symptoms was completed during the two months follow up of the study. The primary outcome was the intensity of menstrual pain, which was determined using the verbal multidimensional scoring System described by (1) and it has 4 grade including grade 0: menstruation is not painful and daily activity is unaffected, grade 1: Menstruation is painful but seldom inhibits normal activity, analgesics are seldom required; mild pain, grade 2: daily activity is affected, analgesics required and give sufficient relief so that absence from school is unusual; moderate pain and grade 3: activity clearly inhibited, poor effect of analgesics, vegetative symptoms such as headache, fatigue, vomiting, and diarrhea.

Statistical analysis

Sample size was computed using $\alpha = 5\%$ and absolute error equal to 0.24 for correlation between medication and pain with acceptable absolute precision formula. A p-value of 0.05 was considered statistically significant. Randomization was determined on a 1:1 basis using random number tables. Statistical comparisons were determined using the Mann-Whitney U test, unpaired t-test, and within-group comparisons were analyzed by paired t test or Wilcoxon.

Ethical evaluation

Participation in the study was voluntary and the participants were free to withdraw from the study whenever they wished. An informed consent was obtained from all participants before enrolment into the study.

Results and discussion

As result showed that on table 1, the mean age was 22.1 ± 1.4 and 20.4 ± 1.2 years in aloe vera gel pills and Ibuprofen groups, respectively. No significant difference was observed for the matched characteristics studied between the treated groups.

In term of educational field of study, the higher frequency was seen for the individuals with bachelor science degree. Level in paramedical science (42 out of 100 individuals or 42%) compared to the other groups and in term of educational degree totally. Moreover, 71 out of 100 had bachelor science degree in all medical sciences (71.00 %), including medical students who only were 20 out of 100 (20%). Chemical medication was the most common method used by the participants in both groups as the pain relief procedure before interventions applied by the current clinical trial. The subjects were followed up at least for two sequential periodic cycles. The pain grades were similar in both groups before intervention. About 3 h after the intervention at the first day of menstruation the mean pain grade amongst aloe vera group was decreased from 2.81 ± 0.65 to 2.02 ± 0.34 , while in Ibuprofen group from 2.48 ± 0.4 to 1.32 ± 0.15 , respectively, using the described given dose.

The pain grade was 1 and higher before intervention in both groups, while it reached zero in about 20% of the individuals of aloe vera group and 17% of those in Ibuprofen group 6 h after the intervention so that they did not ask any more interventions (Table 2).

The comparison of the pain duration between the two groups at the first month of the intervention is shown in Table 3. There was no statistically significant decrease in pain duration for the women who received Ibuprofen compared to those who used aloe vera. Also there was no significant difference in pain grade between the groups at the second month of intervention ($p=0.61$). Pain duration at the second month of trial was similar between the both groups ($p=0.76$). Furthermore, the duration of menstrual flow was similar between the two groups before intervention, while Ibuprofen reduced the duration of menstruation compared to the aloe vera at the first and the second month of the intervention. The present results suggested that the both aloe vera and Ibuprofen group had equivalently reduced the grade and the duration of menstrual pain. The effects of aloe vera as an herbal pain killer can be attributed to the reduction of PG synthesis by its action as an antispasmodic and anti-PG. Studies show that β -adrenoreceptors activation in uterus causes relaxation (8) and a stimulatory effect of *Z. multiflora* Boiss extract has been shown on β_2 -adrenoceptors, which is perhaps due to its

constituent, carvacrol (Boskabady et al., 2006). Ozgoli et al., (2009) (13) mentioned that there were not significant differences between groups in baseline characteristics, $p > 0.05$. At the end of treatment, severity of dysmenorrhea decreased in all groups and no differences were found between the groups in severity of dysmenorrhea, pain relief, or satisfaction with the treatment, $p > 0.05$. No severe side effects occurred. Khazaiyan and Navidian (2012) (12) showed that there was a significant difference between aloe vera and placebo groups concerning the intensity of pain, number of Analgesics and amount of bleeding, but no significant difference was observed regarding the side effects.

Conclusion

Management using anti-inflammatory drugs and analgesics is often an unsatisfactory answer due to side effects and patient compliance issues. The results of this study suggested that the aloe vera gel pill as a novel herbal pain killer represents an effective treatment for the menstrual pain with no important side effects, although further clinical trials are recommended to look at the possible side effects in an extended spectrum of subjects. The study showed that herbal pills are effective for relieving the severity of pain also. Therefore, health-care providers should consider it as treatment for young women with primary dysmenorrhoea problem. Additionally, future studies are recommended to test the feasibility and effectiveness of this kind of herbal therapy in large segments of population for more explanation.

Conflict of interests

There is no known conflict of interests associated with this paper and there has been no significant financial support for this work that could have influenced its outcome.

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Table 1. Comparison of characteristics between experimental groups

Characteristic	Group	n	Mean ± SD	P-Value
Age	Aloe vera gel pill	65	22.1±1.4	n.s
	Ibuprofen	42	20.4±1.2	n.s
Age incidence of dysmenorrhea	Aloe vera gel pill	65	15.6±1.7	n.s
	Ibuprofen	42	15.1±1.8	n.s
Duration of cycle	Aloe vera gel pill	65	28.2±1.6	n.s
	Ibuprofen	42	27.1±1.6	n.s
Duration of menstrual flow	Aloe vera gel pill	65	5.1±1.7	n.s
	Ibuprofen	42	4.9±1.5	n.s
Pain duration	Aloe vera gel pill	65	3.5±0.9	n.s
	Ibuprofen	42	3.2±0.6	n.s

*SD = Standard deviations; n.s=**no significant.

Table2. Comparison of pain relief between different groups before intervention

Treatments	Aloe Vera gel pill		Ibuprofen		P-Value
	n	percentage	n	percentage	0.865
Chemical medicine	40	40.3	31	27.5	
Herbal medicine	15	12.5	14	15.4	
Others treatments	15	10.4	10	7.5	
Total	70	63.2	55	45.4	

Table 3. Comparison of pain duration in aloe vera gel and Ibuprofen groups at various time points following intervention.

Treatments	Aloe vera gel pill	Ibuprofen	Total %
	n %	n %	
Less than 0.5 h	13 (19)	10 (18.1)	23 (18.5)
0.5 - 1 h	22 (44.5)	17 (49)	39 (46)
Several hours	18 (34)	10 (29)	28 (36)
Total	43 (100)	37 (100)	90 (100)

Pathogenetic mechanisms of affiliation generalized parodontal diseases and anorexia nervosa

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Abstract

Introduction. Diseases of parodontal tissues occupy a leading place in the structure of dental diseases. Early diagnosis of the initial degree of generalized parodontitis (GP) is an effective way of secondary prevention. This is due to the complexity of understanding the etio-pathogenetic mechanisms of the development generalized parodontal diseases (GPD) and the high association of them with a number of diseases of the internal organs and systems with common points of contact between interdependence and mutual influence, in particular with anorexia nervosa (AN). Recently, the incidence of AN has increased significantly and poses a serious state, social, psychological and medical problem. There are serious changes on the axis hypothalamus - pituitary - amygdala, genital and thyroid glands, which cause a decrease in thyroid hormone metabolism, cause hypogonadism, secondary hyperparathyroidism due to AN. The detection of tissue sensitization to bone antigen can be an adequate specific reaction for early diagnosis of GP. **Objective.** To establish the features of configuration of generalized parodontal diseases and their clinical manifestations in the format of basic characteristics of anorexia nervosa. **Material and methods.** Clinico-radiological, immunological, analytical and statistical methods were used. Objects were 75 patients with AN, aged 18-36 years (average age 26 ± 3.8) - the main group (M), and 60 patients with GPD without signs of anorexia of the same age - comparison group (C). For a detailed analysis of the clinical manifestations of clinical manifestations of GPD in patients with AN, all patients in the main (M) and comparative (C) groups were divided into several subgroups. M₁ subgroup - patients with various forms of gingivitis. The M₂ subgroup was presented with patients with generalized parodontitis (GP) with AN as the basic pathology. The comparative (C) group consisted of two subgroups (C₁), (C₂) with different forms of gingivitis and GP, respectively. The control group consisted of 30 people similar to the age and sex without clinical signs of periodontal disease. Diseases of internal organs and systems, including the osteoarticular apparatus, in these examined people were excluded. **Results.** A high incidence of GPD up to 100% was diagnosed, including both independent parodontal soft tissue disease and all components of the parodontal complex, which had characteristic of all age groups and varied with patient age, duration of AN and its stages. Among the independent forms of gingivitis, the most common was chronic catarrhal marginal gingivitis ($86.7 \pm 8.8\%$), with some cases of exacerbation on the background of the overwhelming absence of complaints with single manifestations of agrarian, complexity of psychological alliance. GP was predominantly I-II degree, with chronic course prevailing over other forms of GPD ($80 \pm 4.6\%$). Radiographically, in all patients, regardless of the severity of GP, there was an extension of the parodontal cleft and osteoporosis of the bone component of the parodontal complex, horizontal type of resorption. Advantages and priorities of different segments of parodontal complex lesions in patients with AN were not observed. For all patients with GP, a high degree of tissue sensitization to the bone antigen, characterizing significant changes in the bone component of the parodontal complex with AN, was finalized. **Conclusions.** Thus, direct correlation and interdependence of generalized parodontal diseases in the format of basic characteristics of anorexia nervosa were established.

Key words: *generalized parodontal diseases, generalized parodontitis, hypersensibilisation, anorexia nervosa, osteoporosis,*

Introduction

Diseases of parodontal tissues, including generalized parodontitis (GP), consistently occupy one of the leading places in the structure of dental diseases (1). Thus, according to recent epidemiological studies, the prevalence of GP is 60-100% with a persistent

tendency to increase the frequency of GP in young and employable people with gender and population preferences (2). This circumstance causes serious concern of state, social, medical and scientific institutions.

Despite the increase in dental culture of the population, which has been trending lately and prompts the early treatment of patients, the result of treatment of generalized parodontal diseases (GPD) is often unsatisfactory. This is due to some extent because of the complexity of understanding the etio-pathogenetic mechanisms of development of these diseases, and the high association of GPD with a number of diseases of the internal organs and systems with common points of contact between interdependence and mutual influence (3).

A great number of researchers point to the high probability of pathogenetic communication of GPD with endocrine pathology, systemic diseases of human connective tissue, infraction vitamin, protein and lipid metabolism, emphasizing the thesis of associativity, affiliation and, even, the comorbidity of these diseases in patients with such basic pathology (4, 5, 6, 7). But in literature there are only fragmentary science articles that suggest a possible correlation of anorexia nervosa (AN) and GPD and offer a specific approach to the features of their treatment, which, in our opinion, is a major drawback (8, 9, 10, 11).

Recently, the incidence of AN has increased significantly and poses a serious state, social, psychological and medical problem. According to WHO in the general population, the prevalence of AN ranges from 0.37 to 1.0 per 100,000 population, with a frequency of 0.9- 4.3% in women and 0.3% in men and tends to increase significantly (12, 13, 14, 15). A particularly high risk of death was found with critically low body weight and later onset (16, 17, 18, 19, 20).

There are significant changes, associated with AN, in the neuro-endocrine system, including the axis of the hypothalamus - pituitary - amygdala - genital and thyroid gland (21, 22, 23, 24). These changes are accompanied by a decrease in estrogen production, leading to pre-menarcheal amenorrhea and potentiating cortisol levels, abnormal secretion of insulin-like growth factor-1 and decreased thyroid hormone metabolism (25, 26, 27, 28). Hypoestrogenia can be a trigger for the development of osteopenia and osteoporosis, which leads to a decrease in bone mineral density (29, 30, 31). Emerging hypogonadism and secondary hyperparathyroidism, as a result of disorganizing eating behavior in AN, low calcium intake, and vitamin D deficiency and hypercorticism, may also be one of the important components that predispose GPD in patients with AN (32, 33, 34, 35, 36, 37).

Absence of clear ideas about interaction and interaction do not allow to develop adequate methods of treatment of GPD in patients with AN.

It should be noted that clinical, radiologic, as well as laboratory diagnostics of advanced degrees of GP is not a problem. At the same time, the diagnosis of GP at the initial degree presents certain difficulties. Thus, the absence of clear markers which identify initial changes in the key moment of initiating the debut of the pathological process in GP, makes it difficult to diagnose and, as a result, to conduct opportune in full and adequate treatment. This circumstance often leads to the fact that the initial degree of GP is accepted and identified with different forms of gingivitis. As a result, the current treatment is directed to stopping, first of all, the inflammation process in the parodontal tissues in order to reduce the activity of osteoclasts without the inclusion of funds that normalize the metabolism of the bone tissue of the alveolar process.

Standard indicative criteria for the condition of the alveolar process, for example, the level of calcium, copper, strontium in blood plasma, bone-specific alkaline phosphatase, cholesterol, triglycerides of blood serum, oxyproline plasma, bone mineral density are quite burdensome for patients and are nonspecific indicators under impact of many components of the body, which makes it difficult to use, complicates the interpretation of the facts. In our opinion, the determination of tissue sensitization to bone antigen can be that adequate specific reaction that could help for early diagnosis of GP.

Aim: To establish the features of the configuration of generalized parodontal diseases and their clinical manifestations in the format of basic characteristics of anorexia nervosa.

Tasks:

1. To establish frequency, clinical and radiological markers of generalized parodontal diseases in patients with anorexia nervosa.
2. To study the degree of cooperation of age, gender, duration and form of anorexia nervosa with generalized parodontal diseases.
3. To determine tissue allergy to bone antigen in patients with generalized parodontal diseases and anorexia nervosa.
4. To present our view of the paradigm of interaction of affiliation and comorbidity of generalized parodontal diseases and anorexia nervosa.

Materials and methods: to achieve this goal, clinical and radiological methods of parodontal assessment were used to verify the diagnosis (according to the systematics of parodontal diseases after M.F. Danilevsky, 1994) as well as immunological tests (inhibition of migrating leukocytes) by M. George method as a first type screening reaction and statistical methods which were performed in the SPSS STATISTICA 6.0 and MS Excel 2010 (license number K9366093I 2016). Statistical analysis of the data included the calculation of mean values, standard deviation, and mean error.

Evaluation of tissue sensitization to bone antigen was determined in the inhibition of leukocyte migration (RILM). In RILM reaction, water-salt extract of bone tissue of group 0 (I) Rh (D) was used. The migration index was calculated by the formula:

$$IM = \frac{\text{migration area with antigen}}{\text{migration area without antigen}}, \quad (1)$$

where IM, equal to 0.1-0.5, was corresponded to a high degree of sensitization. The reaction was taken 24 hours after blood collection.

The use of RILM was due to its high specificity and informativeness. It is included in the list of reactions recommended by WHO. Taking into account that the reaction was carried out outside the body (in vitro), conditions were created for multiple examination of the patient for diagnosis and at the stages of treatment.

The research was carried out in compliance with the principles of bioethics and the rights of the patient in accordance with the Helsinki Declaration (2000) and the Fundamentals of Ukrainian legislation on health care (1992).

The object of our research, with informed consent, included 75 patients with AN, 18-36 years (average age 26 ± 3.8) - the main group (M), and 60 patients without AN of the same age - the comparison group (C). For a detailed analysis of the clinical manifestations of GPD all patients in the main (M) and comparative (C) groups were divided into several subgroups. M₁ subgroup - patients with various forms of gingivitis. The M₂ subgroup included patients with generalized parodontitis (GP), associated with AN as the basic pathology.

The comparative (C) group consisted of two subgroups (C₁), (C₂) with different forms of gingivitis and GP, respectively.

All patients with AN had a treatment in the neuropsychiatric department of Kiev Clinical Hospital on railway transport №1 (head of the Department – O.V. Moskalenko). Note, that all examined patients had a restrictive form of AN. We did not have patients with the cleansing form of AN. The control group consisted of 30 people similar to the age and sex without clinical signs of parodontal disease. Diseases of internal organs and systems, including the osteoarticular apparatus, in these examined people were excluded.

Results of own research.

The research, as a whole, established a high incidence of GPD in patients with AN, including both independent soft parodontal tissue diseases and diseases of the entire parodontal complex (table 1).

Table 1 - Basic design of generalized parodontal diseases in patients in the main and comparative groups

Groups of patients	Independent forms of gingivitis (without detailing the form and a course of disease), number of patients (%)	Generalized parodontitis (without detailing the degree and a course of disease), number of patients (%)
The main group	15 patients 20±4,6%	60 patients 80±4,6%
The comparative group	48 patients 80±5,2%	12 patients 20±5,2%

In the result of the research, independent parodontal soft tissue diseases of various forms and the course of gingivitis were diagnosed in 20±4.6% cases, while GP of different degrees and course was observed in 80±4.6% in the main group.

It should be noted that patients of the comparative group without manifestations of anorexia nervosa had a higher incidence of independent forms of gingivitis - $80 \pm 5,2\%$, while GP of different degrees and course was diagnosed less frequently and was observed in $20 \pm 5,2\%$ of cases.

Analyzing the data of patients of the subgroup M₂, catarrhal gingivitis prevailed among the independent diseases of the soft parodontal tissues, while other forms of gingivitis were not diagnosed.

It was found that the majority of patients had catarrhal gingivitis in $86.7 \pm 8.8\%$ cases, which had exclusively chronic course, and exacerbation of the process was observed only in $13.8 \pm 8.8\%$ cases.

It is fair to note that the collection of a detailed anamnesis in patients of the main group and the identification of complaints was difficult due to the lack of a psychological alliance, which was accompanied by a lack of willingness to participate in voluntary contact during the examination. This is due to the fact that people with AN are unreliable "informants". Only a further structured interview helped gather information to evaluate anamnestic features and complaints.

While examination patients of the (C) group collection of anamnesis and complaints had no difficulties. Such patients were ready for dialogue. There was an open desire to participate in a therapeutic alliance.

We believe that the absence of any connotative dental complaints in patients of (M) group, in our opinion, could be due to the full focus only on the paradigm of their appearance, pathological concern about their own weight, figure and low level of all components of compliance. But in $20 \pm 10.3\%$ of cases there was a so-called symptom of aeration, manifested by complaints of the inability to chew food, unbearable pain when trying to bite off a piece of fresh bread, "pathological tooth mobility" and a feeling of tooth loss that did not respond to clinical changes.

It should be noted that in the majority of patients of M_1 subgroup chronic gingivitis was characterized by involvement in the pathological process of only the marginal part of the gums. In most cases ($66.7 \pm 12.2\%$) with a background of stagnant hyperemic and dense gums, a marked narrow band of stagnant hyperemia was noted in the area of the cervical teeth. In $20 \pm 10.3\%$ cases areas of congestive gum hyperemia were replaced by zones with marked pallor. It was found that only $13.8 \pm 8.8\%$ cases of chronic inflammation covered all components of the soft tissues of the periodontium.

Patients in M_1 subgroup had typically supragingival dental calculus, and in $26.7 \pm 11.4\%$ cases it appeared as a whole layer.

In all patients of the M_1 subgroup according to the radiological examination, the extension of periodontal fissures was established throughout, while maintaining the cortical plate. They noted osteoporosis of the apex of the alveolar bone ridge and bone components of the parodontal complex.

It can be assumed that the enlargement of the periodontal cleft and osteoporosis, on the one hand, was due to chronic inflammatory process in the soft

tissues of the parodontum, and on the other - the existing osteoporosis could be a manifestation of systemic osteoporosis caused by a decrease in estrogen production, abnormal secretion of insulin secretory factor and decreased thyroid hormone metabolism, resulting hypogonadism, and secondary hyperparathyroidism.

Patients of the C_1 subgroup, unlike patients of the M_1 subgroup, were diagnosed with all forms of gingivitis, including catarrhal, atrophic, desquamative, ulcerative-necrotic and hypertrophic, accounting for $77.1 \pm 6.1\%$ cases, $4.2 \pm 2.9\%$ cases, $6.3 \pm 3.5\%$ cases, $2.1 \pm 2.1\%$ cases, $10.4 \pm 4.4\%$ cases, respectively.

It should be noted that, unlike the patients in the (M) group, in the (C) group, a high motivational component was observed, which indicated a willingness to take part in full treatment.

Finalizing the analysis of subjective and clinical manifestations of lesions of parodontal soft tissues affiliated with AN, the patients of the (M) group were characterized by:

- no complaints;
- low degree of psychological alliance with the doctor;
- had catarrhal gingivitis with a predominant lesion of the marginal gums with chronic course;
- extension of the periodontal cleft and osteoporosis of the bone component of the parodontal complex.

In 60 patients ($80.0 \pm 4.6\%$) (out of 75) of the (M_2) subgroup on the basis of clinical and radiological examination was diagnosed GP from the initial to the second degree, chronic course with the predominant absence of complaints (table 2).

Table 2 - The distribution of parodontal lesion in patients with anorexia nervosa

Group of patients	GP, initial-I degree, chronic course	GP, I-II degree, chronic course
The main group	12 patients $20 \pm 5.2\%$	48 patients $80 \pm 5.2\%$

It should be noted that among the examined patients of the M_2 subgroup, GP had a chronic course, and only $3.3 \pm 2.3\%$ cases had exacerbation of the process as a result of the recently transmitted infectious process. Symptomatic catarrhal marginal gingivitis was observed in soft parodontal tissues. We believe that mainly chronic course of GP in patients of M_2 subgroup, in our opinion, could be caused by significant changes in the general

immunological reactivity of the organism due to AN, which did not allow to trigger an active inflammatory response.

As a result of radiological examination of patients of M₂ subgroup with primary –I degree GP, the extension of the periodontal fissure and osteoporosis of the bone component of the parodontal complex was revealed, the horizontal type of resorption in all patients, as well as the cortical plate dislocation in the segment of the primary degree, and 1/3 reduced in the segment I degree. The advantages and priorities of different segments of the parodontal complex in patients with AN were not observed.

In determining the hypersensitivity of the delayed action to the bone antigen in this group, all patients showed a high degree of tissue sensitization, which showed significant changes in the bone component of the parodontal complex. This could be a predictor and an indicative factor that simplifies the diagnosis of initial -I degree, GP when the radiographic picture is not yet clearly expressed (table 3).

Table 3 – The frequency of tissue sensitization to the bone antigen in patients with generalized parodontal diseases and in almost healthy people

Groups of patients	Diagnosis	Tissue allergy	
		The number of patients	Bone antigen (inhibition of migrating leukocytes*)
The main group	GP, initial -I degree, chronic course	12	16,7±4,4
	GP, I-II degree, chronic course	48	66,7±5,6
	Generalized catarrhal gingivitis, chronic course	13	5,6±2,7
The comparative group	GP, initial -I degree, chronic course	9	15±4,6
	GP, I-II degree, chronic course	3	5±2,8
	Generalized catarrhal gingivitis, chronic course	35	8,3±3,6
The control group	Almost healthy	30	0

* - % positive reactions

We would like to note, that in no case in the patients of the control group tissue sensitization to the bone antigen was not established.

Some peculiarities were established in the research of the interdependence of GPD and AN with the gender of patients, age and their peculiarities of duration, form and stage of the main disease.

Thus, no influence of gender on the peculiarities of manifestation of GPD, associated with AN was noted (fig 1).

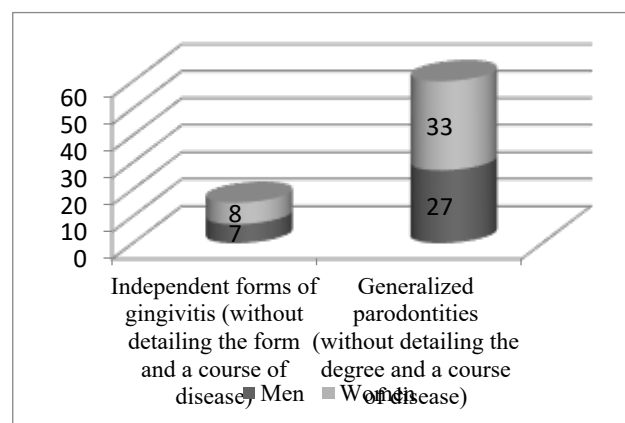


Fig. 1- The impact of patient's gender with anorexia nervosa on the features of the course of generalized parodontal diseases

It was found that high frequency of GPD was defined to all age categories of patients with AN, and the course of GP increased with age (table 4). It should be noted that since the exacerbated course of both catarrhal gingivitis and GP was observed in 2 persons, respectively, we considered it expedient to analyze the effect of patients' age on the frequency of GPD only among persons with GPD chronic course, associated with AN.

Table 4 - Influence of age on frequency of generalized parodontal diseases in patients with anorexia nervosa

Main disease	Age of patients, years	Catarrhal gingivitis, chronic course	Generalized parodontal diseases	
			GP, initial-I degree, chronic course	GP, I-II degree, chronic course
Anorexia nervosa	18-25	7 9,9±3,5% p > 0,05	8 11,3±3,8% p > 0,05	11 15,5±4,3% p > 0,05
	25-30	4 5,6±2,7% p > 0,05	3 4,3±2,4% p > 0,05	16 22,5±5% p > 0,05
	31-36	2 2,8± 2% p < 0,01	1 1,4±1,4% p > 0,05	18 25,4±5,2% p > 0,05
Total		13 18,3±4,6%	12 17,1±4,5%	45 63,4±5,7%

*p – confidence indicator

It is established that as the stages of AN progress, in particular primary, anorectic and cachectic, the proportion of people with GP increases. Thus, if it was 14.7% at the initial stage of AN, and reached 20% at the anorectic stage, then it was already 42.7% at the cachectic stage (fig.2).

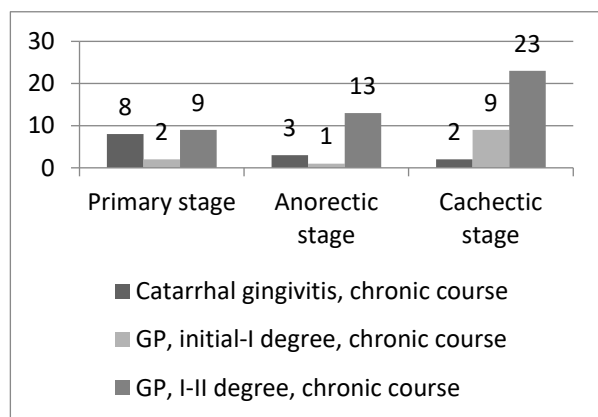


Fig 2. Influence of stages of anorexia nervosa on the frequency of generalized parodontal diseases

The results of the research showed no correlation between the duration of AN and the independent forms of gingivitis, but a direct dependence of the underlying disease and GP was found more with accentuation for the duration of 9-12 years (table 5).

Table 5 - Influence of the duration of anorexia nervosa on the manifestation of generalized parodontal diseases

Duration of anorexia nervosa, years	The number of patients	Catarrhal gingivitis, chronic course	Generalized parodontal diseases	
			GP, initial-I degree, chronic course	GP, I-II degree, chronic course
1-3	15	4 5,6±2,7% p > 0,05	3 4,2±2,4% p > 0,05	8 11,3±3,8% p > 0,05
4-8	19	5 7±3% p > 0,05	2 2,9±2% P > 0,05	11 15,5±4,3% P > 0,05
9-12	37	4 5,6±2,7% p < 0,01	7 9,9±3,5% p > 0,05	26 36,6±5,7% p > 0,05
Total		13 18,3±4,6%	12 17,1±4,5%	45 63,4±5,7%

As a result of our study, we have formed a view regarding the interaction of affiliation and comorbidity of generalized parodontal diseases and anorexia nervosa (scheme 1).

Conclusions:

1. A high incidence of parodontal disease was established, reaching 100% in patients with anorexia nervosa.
2. Among the independent forms of gingivitis, the most common was generalized chronic catarrhal gingivitis with an emphasis on the marginal gums in patients with anorexia nervosa.
3. It is established that generalized parodontitis prevails over other forms of GPD ($80 \pm 4.6\%$), mainly I-II degrees, chronic course in patients with anorexia nervosa.
4. The influence of age on the frequency of generalized parodontal diseases has been established. The severity of GP was directly dependent on the age of patients with AN.
5. The course of GP was directly dependent on the age of patients with AN.
6. The relationship between the main clinical and radiological manifestations of generalized parodontitis from the the duration and stage of nerve anorexia (primary → anorectic → cachectic) was established.
7. The revealed tissue sensitization to the bone antigen in patients with GP and AN even at the initial degree requires mandatory inclusion in the general treatment regimen of osteotropic drugs, including preparations of vitamin D₃, which provides differentiation of cells of the alveolar process, potentiation of carbohydrate, lipid metabolism.
8. The hypothesis of a probable paradigm of interdependence of GPD and AN as affiliated diseases is proposed as the first stage of further development of this direction.

Authors declare no conflict of interest.

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Are cardiovascular rehabilitation programs implemented in young patients with acute coronary syndromes following revascularization procedures?

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Abstract

Objectives. The aim of the study was to identify some particularities of young patients with acute coronary syndrome (ACS) related to risk factors, interventional details and differences between sexes. At the same time, the impact of the Anti-Smoking Law in Romania on these characteristics was monitored.

Methods. The study included young patients with ACS treated in the Catheterization Laboratory of the Heart Institute in Cluj-Napoca over a period of 4 years. Risk factors, epidemiological, clinical, biological, ultrasound, interventional findings, and in-hospital evolution were analyzed.

Results. Of all 789 patients, the majority (73.26%) were men. The predominant risk factors were smoking and those related to inadequate nutrition (dyslipidemia and overweight). Most of the patients had simple lesions, treated with a single stent. During the 4 years, a decrease in the number of non-smoking patients admitted for ACS (from 13.87% to 10.86%) was observed, and in-hospital evolution improved.

Conclusion. The main risk factors in young patients with ACS are related to an inadequate lifestyle, particularly smoking. The first beneficiaries of the Anti-Smoking Law in our country are passive smokers. Inclusion of these patients in cardiovascular rehabilitation programs might bring further benefits. More extensive, nationwide studies are required to confirm this fact.

Key words: *acute coronary syndrome, young patients, anti-smoking law,*

Introduction

Although the entire spectrum of acute coronary syndromes (ACS) is characteristic of the elderly population, over the past years there has been an increase in their incidence among young people. This is mainly due to an unhealthy lifestyle: smoking, obesity, inadequate nutrition, sedentary (1). Their incidence in young individuals differs depending on the chosen age limit; up to 10% of the population under 50 years of age (1,2).

The affected young population has a different clinical picture, with fewer comorbidities (arterial hypertension, diabetes mellitus, renal failure), as well as a family history of cardiovascular disease, dyslipidemia, especially familial, and most of the times a smoking status (1-3).

Young men are up to three times more affected, the ratio decreasing with age (4). Young women may develop ACS through different mechanisms: microvascular dysfunction, spontaneous coronary dissection, and the unstable plaques are most frequently caused by erosion and not by rupture (5). Women have more traditional risk factors than men, an atypical presentation, and consequently, they

access medical services at a late stage. Prognosis is often more unfavorable.

The first-line treatment of patients with ACS is percutaneous coronary intervention (PCI). The majority of young people present with an ACS picture which on the 12-lead electrocardiogram does not show persistent ST segment elevation. At the time of angiography, a single unstable lesion is frequently detected (3), which is induced by the rupture of an insignificant soft atherosclerotic plaque that triggers the formation of the platelet thrombus, the main component of the lesion. Hence the particularity of treatment in this case. The association of intense antithrombotic treatment, possibly catheter aspiration, is imperative in the presence of angiographic signs of a considerable thrombus, as well as direct stenting of the lesion in order to avoid distal embolization of the treated vessel. Inclusion of these patients in cardiovascular rehabilitation programs is essential not only for increasing of their effort capacity, but also for a stricter control of cardiovascular risk factors and lifestyle modification.

Material and methods

The study included young patients with ACS addressed to the catheterization and angiography laboratory of the Heart Institute in Cluj-Napoca in the period 2015-2019 and in whom stenotic coronary lesions of at least 50% were detected, with an indication of revascularization.

The age limit was 50 years for men and 55 years for women. All the medical data from our service was evaluated for the presence of cardiovascular risk factors, electro-cardiographic, echocardiographic, angiographic changes and the treatment used (including interventional treatment).

The analyzed risk factors were: arterial hypertension (HTN), dyslipidemia, obesity (BMI), diabetes mellitus (DM) and smoking.

We did an in-depth analysis of the lipid profile: total cholesterolemia, LDL-cholesterol, HDL-cholesterol and triglycerides levels.

The smoking status was considered non-smoker if the patient did not smoke at all in the last 10 years and former smoker if they had. Active smokers were considered all the patients which were smoking on daily basis at the time of ACS.

From an electrocardiographic and biological point of view, the type of coronary syndrome was assigned to the three categories: ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP), and STEMI was classified depending on the location of the infarction territory.

Thus, we comparatively analyzed, over the 4 years, the data collected from the intervention files and the medical records: the first year – before the introduction of the Anti-Smoking Law in Romania (March 2016), the following year (April 2016 – April 2017), the transition year, immediately after the introduction of the law, and the last two years (April 2017 – April 2019).

In this context, we aimed to evidence the possible impact of the mentioned law on the percentage of young smokers, as well as the changes in the analyzed parameters over time.

These patients were not included in cardiovascular rehabilitation programs.

The study was approved by the Hospital Ethics Committee, all participants in the study signing an informed consent.

Microsoft Office Excel and SPSS v.20.0 statistical software was used for data management and analyses.

Results

General data

The general characteristics of the patients are synthesized in Table I. Of the 789 patients enrolled, the majority were men (73.26%), with a mean age of 44.59 ± 4.84 years. The mean age of women was 47.65 ± 6.15 years. From a demographic point of view, 60% of the patients came from urban areas; about half of these from Cluj county, and a quarter from the border counties: Alba, Sălaj and Bistrița-Năsăud (in order of prevalence). Regarding the risk factors found, smoking had the highest incidence, almost 90% of the patients being active smokers or former smokers. The great majority of the patients had dyslipidemia (85%) or a high BMI, over 25 kg/m^2 (80%). About half of the patients were hypertensive (51.96%), and a small proportion were diabetic (16.6%). Among women, there was a lower incidence of the different types of dyslipidemia, overweight and smoking, and a higher incidence of hypertension and diabetes mellitus – Table I. The evolution of smoking status over the years is synthesized in Figure 1. We noticed a trend of a percentage reduction of the non-smokers patients with ACS during the years.

More than half of the enrolled patients (55.70%) presented STEMI: men - 58.82% vs women - 46.92% ($p=0.002$) (Table II). Women had NSTEMI in a significantly higher proportion - 53.08% vs 41.18% ($p=0.002$). With regard to the location of STEMI, 52.16% were in the anterior territory, followed by those located in the inferior territory (32.35%) and those in the lateral territory (15.49%). Of the biological parameters recorded, most of the patients had leukocytosis, a small proportion had anemia (6.5% in men vs 10% in women) and thrombocytosis (5%). A higher percentage of women (16.34 % vs 4.90%) had some degree of renal dysfunction according to the cut-off value of serum creatinine in our institution (serum creatinine was considered to be normal at values of less than 1.2 mg/dl for men and 0.9 mg/dl for women) (Table I).

Interventional data

The main data related to the performance of the interventional procedures are shown in Table II. The great majority of the patients (86.4%) investigated in our laboratory underwent percutaneous revascularization; a small proportion (4%) underwent surgical revascularization, by aortocoronary bypass, and 9.5% of all patients were medically treated. Conservative treatment was indicated in a significantly higher proportion of

women compared to men - 14.22% vs 7.79%, $p=0.006$. These patients could not undergo revascularization because of severe diffuse involvement, or they refused surgery. The predominantly used approach was the radial approach (80%). Approximately half of the patients had a single vessel affected, resolved in the same session; a quarter had two vessels affected, and the rest had 3 or more vessels affected. Also, about 50% had a single lesion, and a quarter had 2 severe lesions on initial angiography. The majority of the lesions were stenotic (64.13%), particularly among women. These also had the left main coronary artery (LM) and the left anterior descendent artery (LAD) affected more frequently supplying a bigger amount of myocardium, while men had more frequent circumflex artery (CX) and right coronary artery (RCA) involvement. In three quarters of the patients, a single stent was used. The use of drug-eluting stents definitely increased over the years, from 65% to 93%. The mean length of the stents used was 29.85 ± 16.09 mm, slightly longer in women and the mean diameter was 3.07 ± 0.40 mm in women and 3.24 ± 0.45 mm in men, the later with a statistical significance ($p=0.0001$). Thrombus aspiration was seldom used (13.43%) only in patients with STEMI, more frequent in men ($p=0.035$).

Table III synthesizes the medication recommended at discharge. It can be seen that most of the patients had cardio-protective medication: aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors, without any differences between sexes. Ticagrelor was more frequently prescribed in men, while clopidogrel was more often prescribed in women. Eighty-three percent of the patients had a favorable evolution during admission, constant over the years. The mean in-hospital death rate was 3.16%.

DISCUSSIONS

ACS represents the main cause of morbidity and mortality worldwide and its incidence will continue to increase, especially in developing countries (6). In Europe, cardiovascular diseases represent the main causes of death: 40% in men (19% - ischemic heart disease) and 49% in women (19% ischemic heart disease) (7). Cardiovascular diseases are the main cause of mortality in Romania. Of these, acute coronary syndromes (ACS) are responsible for more than half of the deaths. The RO-STEMI (Romanian ST-Elevation Myocardial Infarction) registry enrolled 15076 STEMI patients with a mean age of

62.7 ± 12.7 years from 19 interventional centers and 45 non-interventional centers. Seventy percent were males (8). The main risk factor detected was arterial hypertension, but among young people under 50 years of age, tobacco use was found in more than 70% of the patients (8). Among our cases, in patients under 55 years of age with ACS, the main risk factor detected was smoking, followed by dyslipidemia and body overweight. It should be emphasized that these risk factors are most of the times reversible by using monitoring programs, recommendations and lifestyle changing interventions. Smoking is the most frequent risk factor in young coronary patients. This is responsible for 10% of the deaths of cardiovascular cause according to the latest data provided by the World Health Organization (9). Hence the efforts made at international level to stop this scourge. Among young people, the prevalence of smoking, either active or passive, is the highest. Fournier et al. reported a proportion of 92% smokers among young persons under 40 years of age with acute myocardial infarction (10). Another study conducted by Panagiotakos et al. showed the fact that young smokers have an up to 6 times higher risk to develop myocardial infarction (11). Among our cases, the proportion of smokers was almost 90%, with the predominance of active male smokers. We aimed to monitor their prevalence among patients with ACS presenting to our service, before and after the introduction of the Anti-Smoking Law in Romania in March 2016. After many years of attempts from different medical societies among others, this law was published by the decision-making authorities in our country. Its beneficial effects can already be observed from various polls and estimations, but for a more accurate determination of these effects, a thorough investigation of statistical data from hospitals across the entire country is required. Many studies have shown a reduction in the number of hospitalizations for ACS after the introduction of public anti-smoking laws in the countries concerned. Pell et al. evidenced a 17% reduction of hospitalizations in Scotland in 2006, after the introduction of the anti-smoking law, compared to a reduction of only 4% reported in Great Britain, where there was no such law at that time (12). In Norway, according to the CVNOR registry data, the decrease in the incidence of ACS was mainly due to the decrease in the prevalence of smoking (13). On the other hand, a study in New Zealand reported that despite the public laws applied, the proportion of young

smokers was about 70% (2). Hence it can be concluded that the main beneficiaries of this law are probably passive smokers, most of which are young people who frequently attend public spaces polluted by cigarette smoke. Passive smoking is one of the most common polluting factors in closed spaces. It was estimated that in 2011, globally, 40% of children and 35% of women were regularly exposed to environmental cigarette smoke, as well as more than 50% of the general population in Eastern European countries (14). In our study, we observed a decrease in the prevalence of non-smokers with ACS over the years, which could be explained by the beneficial effects of the law regarding the reduction of passive smoking in public places, frequently attended by young people. In Ireland, the application of a national ban on smoking in public places promptly led to a 12% decrease in ACS hospitalizations, and two years later, a further 13% decrease was seen (15).

Other risk factors with a high prevalence in our study were dyslipidemia and overweight, the latter being predominant among men. Recent data of the EUROASPIRE V study show that in the coronary patients of the 27 countries included in the study, among which Romania, obesity was present in 38%, and low-density lipoprotein (LDL) cholesterol ≥ 70 mg/dL was found in 71% (16). The data of the same study demonstrate that most of the patients had increased LDL cholesterol values (17). In our study, hypertriglyceridemia, lower HDL cholesterol values, smoking and overweight were more frequently found in men, with statistical significance. In contrast, arterial hypertension and diabetes mellitus were more frequent in women. In a retrospective analysis using the National Inpatient Sample (NIS), which included young patients under 45 years of age with acute myocardial infarction, young women had a higher prevalence of anemia, chronic lung disease, obesity, peripheral vascular disease, and diabetes. In the case of young men, dyslipidemia, smoking, and alcohol were predominant (18).

Our study shows a slightly increased prevalence of STEMI (55%) among men, STEMI located in the anterior territory being the most frequently found, particularly in women, which corresponds to the involvement of the main arteries (LM and LAD) and to a worse prognosis.

From a technical point of view, PCI procedures have evolved with the optimization of the equipment and materials and the development of new studies that have changed the recommendations (19). The arterial

approach predominantly used in our service was radial, according to the recommendations to reduce local hemorrhagic complications. If in 2014, only 10% of PCIs involved the placement of drug-eluting stents (DES), the following year, these were found in more than half of the procedures, and in the last two years, the percentage of DES was over 90%. The majority of the young patients had a single lesion of one coronary artery, and the proportion of percutaneously revascularized ACS followed an ascending trend from 80% to 90% in the last year. Obviously, the number of thromb aspiration procedures decreased, according to current recommendations (19) being utilized especially in men in accordance with the higher incidence of STEMI between them. A relative estimation of the atherosclerotic load of the coronary tree was intended by quantifying the number of stents and their length per patient. However, there were no detectable differences regarding the stent parameters over the investigated years. Of notice, stent caliber was significantly larger in men than women. A reduction in the rate of percutaneous reinterventions in the young patients was observed over time, possibly in the context of an improvement in the techniques and materials used, of the optimization of treatment, especially with antiplatelet drugs. In this context, a significant decrease in the in-hospital death rate from 4% to 2.5-2.9% was registered. According to the EUROASPIRE V study, the cardio-protective medication prescription rate was: antiplatelets 93%, beta-blockers 81%, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers 75%, and statins 80%. In the current study, except for renin-angiotensin-aldosterone system inhibitors, all medications were recommended in a proportion of over 90% (16). Considering the presence of the above-mentioned cardiovascular risk factors, we emphasize the necessity of cardiovascular rehabilitation programs in these patients due to several advantages. The main benefit is an increase in survival and of the effort capacity of these patients (19). Secondly, sustained physical activity has also proven its advantages on the reduction of cardiovascular risk factors, as it leads to decrease in the values of total cholesterol and LDL-cholesterol, and moreover an increase in the values of HDL-cholesterol (20). Furthermore, it contributes to normalization of blood pressure values in hypertensive patients (21) and to improvement in flow-mediated dilatation (20). Thirdly, performing such programs under surveillance might contribute

to the monitoring of the approach in lifestyle changes used by these patients, which should also be advised to give up smoking (22). Finally, these programs might lead to adherence in the administration of prescribed cardio-protective medication (23). However, rehabilitation programs are globally underused, with a reported percent of only 25-30% among male patients and 11-20% among female patients (24).

Conclusions

The main risk factors in patients under 55 years of age diagnosed with ACS were modifiable, being represented by smoking, dyslipidemia and overweight, in close relationship with an unhealthy lifestyle. The introduction of the anti-smoking law in Romania is salutary, and this study is the first, to our knowledge, which showed its first positive effects, particularly by reducing the effects of passive smoking in young people. There are small differences regarding the clinical characteristics, drug therapy and revascularization management between men and women, which deserve to be considered in order to particularize diagnosis and treatment depending on sex. Correct treatment of these patients both in terms of intervention and cardio-protective medication can improve their long-term prognosis. Inclusion of these patients in cardiovascular rehabilitation programs might bring further benefits, along with the reduction of cardiovascular risk factors and improving the quality of life.

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Table I. General characteristics of the patients

	Total	Men	Women	P value
Mean age±SD	45.41±5.39	44.596±4.843	47.658±6.159	
Hypertension n (%)	410 (51.96)	285 (49.31)	125 (59.24)	0.013
Diabetes mellitus n (%)	132 (16.6)	85 (14.71)	47 (22.27)	0.012
Hypercholesterolemia n (%)	289 (43.48)	215 (44.06)	74 (41.57)	0.567
LDL-cholesterol ↑n (%)	368 (62.37)	278 (64.2)	90 (57.32)	0.127
Triglycerides ↑ n (%)	334 (52.10)	264 (55.93)	70 (41.18)	0.0009
HDL-cholesterol ↓n (%)	430 (63.70)	332 (73.13)	98 (59.39)	<0.001
Active smokers n (%)	551 (82.98)	422 (86.12)	129 (74.14)	0.0003
Former smokers n (%)	32 (4.82)	25 (5.10)	7 (4.02)	0.568
Non-smokers n (%)	81 (12.20)	43 (8.78)	38 (21.84)	<0.001
BMI> 25 kg/m ²	385 (79.55)	295 (84.77)	90 (66.18)	0.000005
Blood urea nitrogen↑ n (%)	60 (7.97)	27 (4.9)	33 (16.34)	<0.001
Anemia n (%)	56 (7.47)	36 (6.55)	20 (10)	0.111
Leukocytosis n (%)	500 (67.11)	383 (69.89)	117 (59.39)	0.007
Thrombocytosis n (%)	39 (5.21)	24 (4.36)	15 (7.54)	0.084

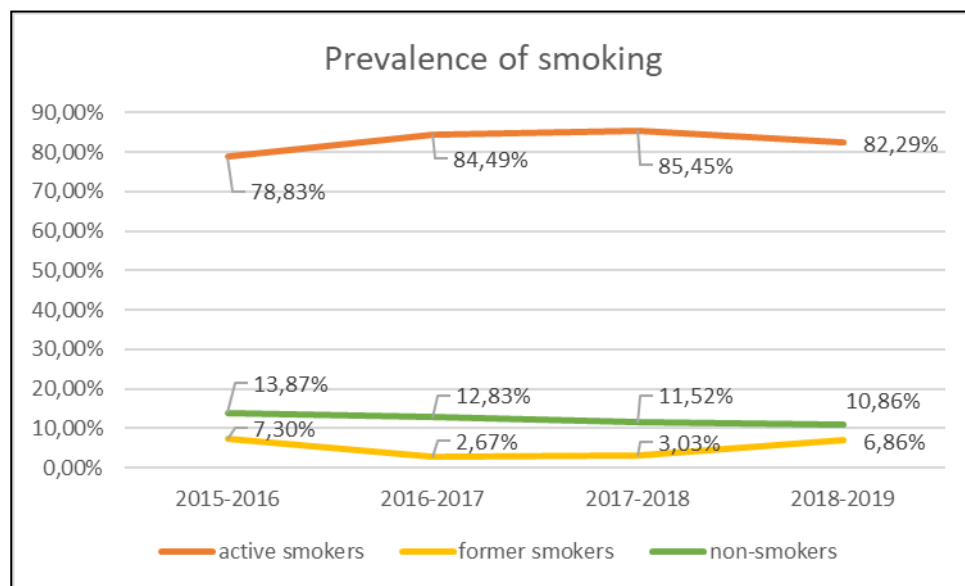


Figure 1. Prevalence of smokers and non-smokers in the period 2015-2019. Patients who quit smoking in the past 10 years, were defined as former smokers

Table II. Types and revascularization treatment of the acute coronary syndromes (ACS) and the variation between men and women.

	Total	Men	Women	P value
<i>Type of ACS n (%)</i>				
STEMI	439 (55.64)	340 (58.82)	99 (46.92)	0.002
ACS without ST segment elevation	350 (44.36)	238 (41.18)	112 (53.08)	0.002
PCI n (%)	682 (86.44)	509 (88.06)	173 (81.99)	0.027
CABG n (%)	32 (4.05)	24 (4.15)	8 (3.79)	0.82
Conservative n (%)	75 (9.51)	45 (7.79)	30 (14.22)	0.006
<i>Acute vessel n (%)</i>				
LM/LAD	403 (51.08)	284 (49.13)	119 (56.4)	0.07
RCA/CX	358 (45.37)	275 (47.58)	83 (39.34)	0.039
<i>No. of vessel n (%)</i>				
1	438 (55.51)	320 (55.36)	118 (55.92)	0.888
2	206 (26.11)	151 (26.12)	55 (26.07)	0.986
≥3	145 (18.38)	107 (18.51)	38 (18.01)	0.871
<i>No. of lesions n (%)</i>				
1	459 (58.17)	340 (58.82)	119 (56.4)	0.54
2	171 (21.67)	119 (20.59)	52 (24.64)	0.22
≥3	159 (20.15)	119 (20.59)	40 (18.96)	0.613
<i>Acute lesion n (%)</i>				
occlusion	283 (35.87)	221 (38.24)	62 (29.38)	0.021
Complete revascularization n (%)	128 (41.96)	94 (42.15)	34 (41.46)	0.914
Aspiration	59	52	7	0.035
Previous revascularization n (%)	93 (11.78)	69 (11.94)	24 (11.37)	0.828
No. of stents/ patient	1.3443	1.1332	1.13744	
No. of DES n (%)	743 (83.11)	550 (84.09)	193 (80.42)	0.593
Stent length (mean±SD)	29.854±16.094	29.284±15.356	31.536±18.002	0.142
Stent diameter (mean±SD)	3.202±0.448	3.248±0.453	3.075±0.409	0.0001

Table III. Medication recommended at discharge

	Total	Men	Women	P value
<i>Treatment at discharge n (%)</i>				
Aspirin n (%)	757 (99.08)	556 (99.11)	201 (99.01)	0.328
Clopidogrel n (%)	316 (41.36)	210 (37.43)	106 (52.22)	0.0002
Ticagrelor n (%)	429 (56.15)	337 (60.07)	92 (45.32)	0.0002
Anticoagulant n (%)	31 (4.06)	23 (4.1)	8 (3.94)	0.921
Statin n (%)	751 (98.30)	551 (98.22)	200 (98.52)	0.593
Beta-blocker n (%)	702 (91.88)	521 (92.87)	181 (89.16)	0.113
ACEI n (%)	615 (80.50)	457 (81.46)	158 (77.83)	0.286
Diuretic n (%)	151 (19.76)	97 (17.29)	54 (26.60)	0.004

Clinicoradiologic aspects of periodontal diseases in patients with gluten-related disorders

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Abstract

Introduction. The frequency of celiac disease (CD) and non celiac gluten sensitivity (NCGS) varies in different geographical area and has gradually increased. CD and has high clinical inhomogeneity. Although it has been suggested that the patient with gluten-related disorders present different oral manifestations. The association between oral manifestation and CD, NCGS is controversial. Often in patients with gluten related disorders in the oral cavity can be found: aphthous stomatitis, desquamative glossitis, angular cheilitis, gingivitis, enamel hypoplasia, xerostomia etc. However in literature there are only few investigation of the association between gluten related disorders and periodontal diseases. **Material and method.** The study included 50 patients with existing periodontal pathology in patients with CD or NCGS aged 18 to 50 years. According to inclusion criteria patient were divided into two main groups (depending on the type of gluten related disorder): I (n=25) patients with CD, II (n=25) with NCGS. Periodontitis was defined according to the standardized procedure. Modified papillary bleeding index (MPBI), Fedorov-Volodkina hygiene index, PMA (papillary-marginal-alveolar index), periodontal probing depth (PD), bone mineral density (BMD) were obtained. **Results and discussions.** Participants of the I study group had a mean age \pm SD 41.03 ± 8.3 years, II - 40.38 ± 8.1 . During the study it was found that in the structure of periodontal diseases general periodontitis were diagnosed predominantly. The mean value of MPBI in the patients with CD was 0.21 ± 0.25 and in patients with NCGS 0.24 ± 0.34 . The Fedorov-Volodkina hygiene index in patients with celiac disease was 1.48 ± 0.3 and with NCGS - 1.51 ± 0.2 . Depth of periodontal pockets in patients of I group was 3.25 ± 1.71 mm., II - 2.88 ± 1.64 mm. The mean PMA index in patients of I group was $28.9\% \pm 15.0$, II - $24.88\% \pm 14.1$. The mean value of BMD in patients with CD range from 1200 to 1300 HU. In patients with NCGS 1100 - 1250 HU. **Conclusions.** The results of this study demonstrate a set of clinicoradiological features of periodontal disease in patient with CD and NCGS. The statistical analysis of the received clinical and radiological data did not reveal statistical differences between the studied groups ($p \geq 0.05$).

Key words: *gluten-related disorders, celiac disease, non celiac gluten sensitivity, periodontal disease,*

Introduction

Periodontal disease is a highly prevalent chronic inflammatory disease affecting of 98% adult population worldwide (1,2). However, according to recent epidemiological studies periodontal diseases affect about 15.2% people aged 20-30 years, rapidly increasing to more than 75% in the group of patients aged 30-40 years (3,4). According to the latest epidemiological findings tendency to increasing the frequency of periodontal lesions among young people has been observed. The problem of diagnosis, treatment and prevention of periodontal diseases in the young individuals remains an important topical issue of modern dentistry and public health system. Progressive periodontal tissue destruction, deepened pocket depths with alveolar bone loss has been observed in patients with generalized periodontitis (5). Accordind it periodontal desease can lead to

early tooth loss in young patient (6).

It is well documented how periodontal diseases are associated with systemic diseases (7,8,9,10). Recent research describe different pathogenic mechanisms of co-relation of chronic periodontal disease and systemic diseases. The main of them describe exposure of dental plaque which entered bloodstream (11,12). Another one describe indirect influence of inflammatory mediators which induced periodontal disease (13,14). Well known is relationship between periodontal disease and diabetes mellitus, cardiovascular, respiratory and gastrointestinal diseases etc (15,16,17,18). Today increasing interest has been directed toward the association of gastrointestinal disease and its manifestations in the oral cavity. Numerous publications underlined that gastrointestinal tract and oral cavity have a close

neurohumoral relationship, because they are different parts of a single morphological system. So 80-87% of patients with gastrointestinal diseases have oral manifestations (19). In recent years decrease attention to oral manifestations of gluten related disorders, especially: celiac disease (CD) and non celiac gluten sensitivity (NCGS) (20,21). According to some studies, specific oral signs and symptoms can be classified as extra-intestinal manifestation of CD or NCGS.

Non celiac gluten sensitivity is not well defined. NCGS is a syndrome of gastrointestinal and extraintestinal manifestations responding to gluten ingestion. Currently, there are no reliable laboratory markers or histological abnormalities. So this diagnosis is more of a diagnosis of exclusion (22,23). Some authors propose another names for NCGS such as: gluten sensitivity, non-celiac gluten intolerance etc (24). However, CD is one the most common T-cell-mediated chronic systemic autoimmune disorders that predominantly affects the small intestinal mucosa in genetically predisposed children and adults as a response to gluten (25,26). The diagnosis is established by a gastroenterologist in accordance with guidelines, based on the finding of serological markers and typical small intestinal villous atrophy (27,28). According to World gastrointestinal organization (WGO) the prevalence of celiac disease significantly increased over the last years is about 1% population worldwide with variety in different countries (29). However, prevalence of NCGS is 5-10% of the total population (30). Despite the level of medical progress, the diagnosis of CD and NCGS is difficult due to the manifestation of the disease, its atypical signs and prevalence of its extraintestinal clinical manifestations. Often in such cases, the diagnostic of this pathology requires a comprehensive and multidisciplinary approach. According to Tortora R. celiac disease is increasingly diagnosed at the age more than 30 years (31). Often in patients with gluten related disorders in the oral cavity can be found: aphthous stomatitis, desquamative glossitis, angular cheilitis, gingivitis, enamel hypoplasia, xerostomia etc. (32,33). However in literature there are only few investigation of the association between gluten related disorders and periodontal diseases. Although, there is a hypothesis that chronic inflammatory process in the jejunum can cause a more severe periodontal disease (34).

The aim of the study. To evaluate the prevalence of periodontal disease in patients with CD and NCGS,

clinicoradiologic peculiarities of manifestations of periodontal disease in patients with celiac disease and non celiac gluten sensitivity,

Materials and methods. The study included 50 patients with existing periodontal pathology in patients with CD or NCGS aged 18 to 50 years. The criteria for inclusion in the study were: the presence of celiac disease or non celiac gluten sensitivity diagnosed by gastroenterologist, the presence of periodontal pathology, adult patients, the patient's consent to participate in the study. Exclusion criteria were: the presence of cancer, the presence of other comorbide pathologies, the absence of patient-doctor compliance, refusal to participate in the study. According to inclusion criteria patient were divided into two main groups (depending on the type of gluten related disorder): I (n=25) patients with celiac disease, II (n=25) with non celiac gluten sensitivity. Clinical examination of patients was performed according to the standard method and included the study of patient complaints, anamnesis morbi and evaluation of periodontal status. Modified papillary bleeding index, Fedorov-Volodkina hygiene index, PMA (papillary-marginal-alveolar index), periodontal probing depth (PD) were obtained. For evaluating bone mineral density, bone loss patients underwent orthopantomogram (Planmeca) and CT (Planmeca). To determine the bone density of the mandible region of interest (ROI) was detected. ROI was constructed at the intersection of three tomographic slices. According to the literature, it is optimal to determine the bone mineral density of the in the area of the second molars of the mandible and chin. The bone density was determined in Hunsfield units (HU).

Periodontal status, periodontal and oral hygiene index, assessment of bone condition were entered into the developed examination card and medical card of the patient. Statistical processing of the obtained indicators was performed using the Mann-Whitney U test, Fisher test using the software «IBM SPSS Statistics 20». $P < 0.05$ was considered statistically significant.

Results and discussions. Participants of the I study group had a mean age \pm SD 41.03 ± 8.3 years, II - 40.38 ± 8.1 . During the study it was found that in the structure of periodontal diseases among patients with celiac disease inflammatory periodontal diseases were diagnosed in 20 % of patients, *dystrophic inflammatory periodontal* diseases in 80%. Dystrophic-inflammatory periodontal diseases were prevalent in patients with NCGS, which was

detected in 72% of patients. During clinical examination of patients with celiac disease, the initial severity of generalized periodontitis was detected in 16 %, the first stage was diagnosed in 27.7% of patients, second - in 50% of patients, and third - in 5.5% of patients. Among patients with celiac disease, 15% of patients had an initial severity of generalized periodontitis, 1 - 20%, 2 - 55% and 10% of patients had 3 stage of generalized periodontal disease. In both study groups, despite the prevalence of the process, a catarrhal form of gingivitis was prevalent, which was diagnosed in 75% of patients.

During the initial examination according to the data obtained in the majority of cases patients in both study groups complained of: gums bleeding, feeling of discomfort, periodic gum swelling. Objective examination of periodontal tissues in patients most often revealed cyanotic (rarely hyperemia) gums and marginal gums, changes in the relief of the gums, gums retraction. The results of determining the presence of traumatic occlusion in patients in groups showed that the prevalence of traumatic occlusion in patients of I and II groups ranged from 70-80%. Depth of periodontal pockets in patients of I group was 3.25 ± 1.71 mm., II - 2.88 ± 1.64 mm. No significant difference was found between two study groups (Mann Whitney test value $U=159$, $p=0.5$). In both study groups, isolated cases with I-II grade tooth mobility were detected. The mean PMA index in patients of I group was $28.9\% \pm 15.0$, II - $24.88\% \pm 14.1$. No significant difference was found between two study groups ($U = 354$, $p=0.2$). The Fedorov-Volodkina hygiene index in patients with celiac disease was 1.48 ± 0.3 and with NCGS - 1.51 ± 0.2 . All patients presented good oral hygiene levels. The mean value of modified papillary bleeding index (MPBI) in the patients with celiac disease was 0.21 ± 0.25 and in patients with NCGS 0.24 ± 0.34 . No statistically significant difference was found between the groups ($U = 225$, $p = 0.08$).

The radiographs of the two study groups in 90% of cases showed resorption of the interalveolar septum not exceeding 1/2 root length. The mean value of Fuchs index on the mandible in patients with CD was 0.8 ± 0.2 . In patients with NCGS the mean value of Fuchs index was 0.9 ± 0.19 . No significant difference was found between the study groups (U index=166, $p=0.6$). In determining bone mineral density of the mandible in patients with celiac disease, the mean value range from 1200 to 1300 HU. In patients with non celiac gluten sensitivity the

mean value of bone mineral density ranged from 1100 to 1250 HU.

Conclusions. The results of this study demonstrate a set of clinicoradiological features of periodontal disease in patient with CD and NCGS. During examination of the oral cavity patients with celiac disease and non celiac gluten sensitivity become aware of prevalence generalized periodontitis. During the evaluation of the hygiene of the oral cavity, attention is drawn to the fact that the unsatisfactory state of oral hygiene in any of the study groups was not detected. The statistical analysis of the received clinical and radiological data did not reveal statistical differences between the studied groups ($p \geq 0.05$). The data obtained that patients with gluten-related disorders have some factors in the oral cavity that influence the progression of periodontal disease. The abovementioned needs further investigation.

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Functional Exercise Capacity and Quality of Life in Type II Diabetes Mellitus Patients

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Abstract

Assessment of physical capacity is of much interest in people with diabetes mellitus in order to correctly prescribe an exercise program for these patients. Therefore, the aim of this study was to assess the functional exercise capacity and the quality of life in a sample of patients with type II diabetes mellitus.

For this cross-sectional study, 20 consecutive type II diabetic women and 20 age and sex matched healthy controls were recruited. The physical capacity was assessed using the 6-minute walk test (6MWT). There were no significant differences between groups in terms of anthropometric characteristics. Mean age in patients' group was 62.35 ± 5.21 years and in control group 61.82 ± 4.89 years. In the 6MWT, the distance covered by the diabetic patients was 498.56 ± 58.3 meters, significantly shorter than that covered by the control group (601.34 ± 42.5 meters) ($p < 0.05$). The AQoL-4D scores were significantly lower in patients' group compared to controls (0.297 ± 0.089 vs 0.778 ± 0.091). The functional exercise capacity and the quality of life are reduced in patients with type II diabetes mellitus compared to healthy controls.

Key words: functional exercise capacity, type II diabetes, 6MWT,

Introduction

The prevalence of diabetes mellitus is relatively high in the adult population, being an important cause of death in developed countries (1,2). The diabetes symptoms and complications negatively affect the patients quality of life, the physical function, leading to deconditioning and deterioration of overall health status (physical and emotional) (2,3). The exact causes of reduced physical fitness and exercise capacity are unknown. The associated cardiovascular diseases and dysfunctions, accentuated by the chronic low-level inflammation (with increased inflammatory markers such as interleukin-10, 18, tumor-necrosis factor-alpha, adiponectin), overweight and obesity, poor glycemic control, associated with high levels of physical inactivity are some of the factors responsible for the low exercise tolerance and capacity in patients with diabetes mellitus (1,4–9). The decreased lower limb muscular strength and impaired mobility also play an important role in the lower functional capacity, which influences the health-related quality of life in diabetes mellitus patients (10).

The impact of diabetes on the health-related quality of life has been studied and patients with type 2 diabetes mellitus has been shown to have a lower quality of life (11,12). Assessment of physical capacity is of much interest in people with diabetes

mellitus in order to correctly prescribe an exercise program for these patients and to improve the quality of life. Therefore, the aim of this study was to assess the functional exercise capacity and the quality of life in a sample of patients with type 2 diabetes mellitus.

Material and method

For this cross-sectional study, 20 consecutive type II diabetic women and 20 age and sex matched healthy controls were recruited. The inclusion criteria were aged 50 to 70 years, diagnosis of type II diabetes for at least two years, under a pharmacological regimen stabilized for at least five months, living independently. Patients presenting diabetes peripheral neuropathy or severe musculoskeletal disorders were not included.

The physical capacity was assessed using the 6-minute walk test (6MWT). The test was performed on a 30-meter straight corridor with no obstacle, according to the American Thoracic Society protocol (13). The patients walked on a self-selected speed. The distance walked in 6 minutes was recorded. The oxygen saturation was also recorded.

The quality of life was assessed with the Assessment of quality of Life (AQoL)-4D questionnaire. This questionnaire evaluates four dimensions of the health-related quality of life – independent living,

social relationship, physical senses and psychological well-being. The score is ranging from -0.04 (worst possible quality of life) to 1 (full quality of life) (14,15).

The statistical analysis was performed with the MedCalc software. Data were compared between groups, using the Student t-test. The statistical significance was set at $p < 0.05$.

Results

There were no significant differences between groups in terms of anthropometric characteristics. Mean age in patients' group was 62.35 ± 5.21 years and in control group 61.82 ± 4.89 years. All participants were overweight with a mean BMI of 28.87 ± 3.1 kg/m² in patients' group and 27.23 ± 4.2 kg/m² in control group.

All participants performed the 6MWT. None of the women evaluated in this study accused any symptoms that could interfere with the test's results (chest pain, dyspnoea, leg pain or cramps). The distance covered by the diabetic patients was 498.56 ± 58.3 meters, significantly shorter than that covered by the control group - 651.34 ± 42.5 meters ($p < 0.05$) (Figure 1). No significant reduction in oxygen saturation was recorded during and after the test.

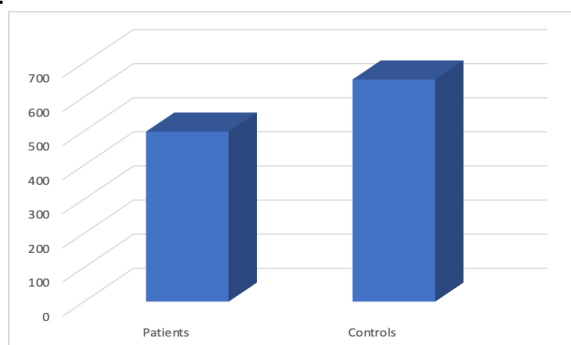


Figure 1. The 6MWT results for patients and controls

The AQoL-4D scores were significantly lower in patients' group compared to controls (0.297 ± 0.089 vs 0.778 ± 0.091) (Figure 2) and were significantly correlated with the distance covered in 6MWT.

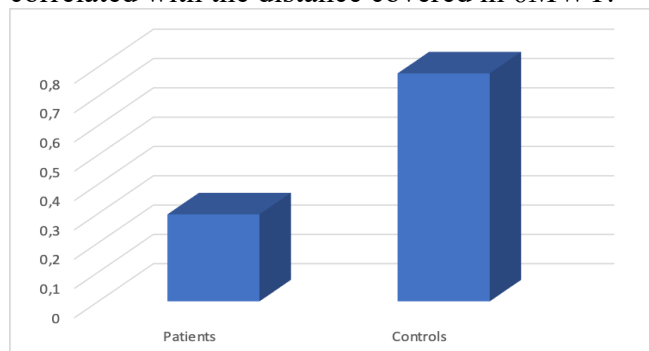


Figure 2. The quality of life results for patients and controls assessed with AQoL-4D questionnaire

Discussion

The aim of the present study was to assess de functional exercise capacity in a sample of patients with type II diabetes mellitus. The results demonstrated a significantly lower functional exercise capacity in diabetic patients compared to healthy age matched controls.

The six-minute walk test is reliable easy-to use test recommended to evaluate the physical function and walking endurance in different adult population with a wide variety of cardio-pulmonary diseases (16–18). The previous studies that used the 6MWT to assess the physical capacity found significant lower distances covered by the patients with diabetes mellitus compared to controls. Kuziemski et al showed that diabetes patients had a 109 m shorter distance covered during the 6MWT than the healthy controls, as well as a pulmonary function (19). Awotidebe et al also found that patients with type II diabetes demonstrated lower functional exercise capacity than healthy controls (20). Similar results were also found by other authors (21–23).

Our results showed a lower quality of life in patients with diabetes mellitus compared to controls, as assessed by the AQoL-4D questionnaire. Similar results were reported in previous studies, a poorer quality of life being associated with adverse outcomes, like disease progression, low response to therapy, mortality (24–26). Health-related quality of life is an important outcome in patients with chronic diseases, assessing multiple domains like physical and mental health, social functioning (27–29).

The functional exercise capacity should be tested in all diabetes patients, with or without cardiovascular associated diseases or complications. Along with the tests used for the exercise capacity testing, balance and muscular strength assessments should also be performed in people with diabetes mellitus (20,30–32). All these will allow a better, individualised exercise programme prescription. Participating in regularly exercise programmes has been proved to have beneficial health effects in all categories of population, younger and older, with metabolic, cardiovascular or musculoskeletal disorders, improving the quality of life and decreasing the mortality (1,33–36).

The limitations of the present study should be noted. The study sample comprised a relatively small number of female patients and this aspect could limit the generalizability of our findings to male diabetes mellitus patients, or to other age groups.

Conclusion

The functional exercise capacity and the quality of life are reduced in patients with type II diabetes mellitus compared to healthy controls. Further studies are needed to identify the risk factors for the low functional capacity in order to improve the quality of life in diabetic patients.

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DIAGNOSTIC ISSUES OF ALLERGIC PHARYNGITIS

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Abstract

This article gives characteristics to the problem of chronic pharyngitis. It describes the lack of modern etiopathogenetic classification, subjective approach to diagnosis, estimates the role of allergic inflammation in the formation of chronic pharyngitis. It was offered a questionnaire revealing the influence of a patient's somatic status on the development of anxiety disorder and depression. We used a diagnostic algorithm for chronic pharyngitis, which includes not only the clinical examination and history, but also a psychosomatic condition questionnaire; CBC, cytological examination of nasal and pharyngeal mucosal secretions, concentration of general and specific IgE; and if necessary, allergy consultation. It can allow an individual approach to the treatment of patients with chronic pharyngitis depending on etiopathogenesis, which will improve their quality of life.

Key words: *chronic pharyngitis, allergy, diagnostic algorithm, questionnaire,*

Introduction

Chronic pharyngitis (CP) is one of the most common pathologies of the upper respiratory tract, which relates to one of the insufficiently explored pathology in modern otorhinolaryngology. CP occupy a leading position in the outpatient practice of otorhinolaryngologists (1). However, the statistics on this pathology are incomplete, as a plenty of patients can be treated by general practitioners, gastroenterologists, neuropathologists, and other related specialists.

In the literature, the term "tonsillopharyngitis" or "pharyngotonsillitis" is widely used (2), although it is absent in ICD-10 and in planned ICD-11.

The etiology and pathogenesis of chronic pharyngitis, which, according to most authors, is a polyetiological disease, are discussed. All existing sources on this subject emphasize that the etiology and pathogenesis of chronic pharyngitis is not well understood. The base of the pathogenesis of CP remains controversial, and today the search for relationships of pathological changes in the upper respiratory tract with the influence of related and concomitant pathology remains relevant (3).

In most cases, acute pharyngitis occurs with acute respiratory viral infection and does not require any treatment, because it passes on its own in a few days, so it is difficult to imagine that the acute process in the oropharynx becomes chronic.

Chronic pharyngitis is an inflammation of the mucous membrane of the upper respiratory tract, has

a slow character and is often difficult to treat. We should emphasize here that the suffix "itis", usually implying an inflammatory pathology, actually covers a number of conditions that are not always associated with infection.

V. Renner et al (2012) give the most concise definition: chronic pharyngitis is inflammation of the oropharynx (4). Often in foreign publications pharyngitis is called "sore throat".

The pharynx is an aero digestive crossroads that participates in the processes of respiration, swallowing, phonation, taste and smell. Therefore, the symptom complex that occurs with this pathology is various and includes: sore throat, sore throat, burning, coughing, choking, feeling a «lump» in the throat, unpleasant aftertaste in the mouth, impaired swallowing, and in some cases, disturbed sleep, appetite, feeling of nervousness. All this reduces the quality of life of the patient and leads to a disturbance of psychosomatic health (5, 6).

Clinical manifestations vary depending on etiopathogenetic factors. The pathogenesis of chronic pharyngitis also includes neurophysiological mechanisms and the mechanism of the L-form of bacteria that cause speech disorders in patients with chronic pharyngitis (7). An individual approach to the treatment of chronic pharyngitis is better than traditional treatment. This is important while choosing a treatment option (8).

There is a single concept of upper respiratory tract diseases that gets widespread recognition. However, most researchers pay attention only to the effect of rhinosinusitis, while ignoring the factors of the pharynx in the lower respiratory tract, especially with the allergic nature of pharyngitis, which has not been fully covered till today (9).

Back in the last century, scientists took an interest in the role of allergy in the pathogenesis of chronic pharyngitis. The most likely symptom in chronic pharyngitis of an allergic nature remains a tickling in the throat, probably of spasmodic etiology comparable to the effect of sneezing. Most likely, it is allergic, since it is not present either with paresthesia of the pharynx of organic origin, or with many dysesthesias that point to a psychosomatic process (10). However, it is still an open question.

Today allergic diseases represent a global health problem that affects 10–25% of the world's population. Pharyngeal symptoms occur in more than 50% of patients with allergic rhinitis (11). Besides the certain types of chronic pharyngitis, this condition is most common in more polluted cities, the causes of which are dust, smoke and industrial pollutants. This can provoke repeated attacks of allergic or vasomotor rhinitis with a secondary infection, catarrhal symptoms in the nasal cavity and recurrent or persistent inflammation of the pharynx. As a result, a condition of increased sensitivity of the mucous membrane of the nose and throat occurs. (12).

There is clear evidence in support of the concept that allergic diseases are influenced by genetic predisposition and environmental exposure (13). Therefore, while taking a patient history, it is necessary to pay attention to a family history.

Modern science distinguishes pathologies of allergic etiology with clinical manifestations in the mucous membranes. Allergic conjunctivitis or conjunctival symptoms are present in 30–71% of patients with allergic rhinitis (14, 15). Eosinophilic esophagitis is considered a specific form of food allergy. Most of these patients also have atopic diseases (asthma, allergic rhinitis, atopic dermatitis). The main symptoms in these diseases are swallowing disorders, pain and discomfort while swallowing saliva or food, burning behind the sternum, belching, and feeling of a «lump» or foreign body behind the sternum (16, 17). In the description of these symptom complexes, lots of symptoms are inherent in inflammation of the pharynx: pain, soreness, burning, swallowing disorders, changes in taste, etc.

In recent years, the term “oral allergy syndrome - OAS” or “pollen-food allergy syndrome” has appeared in the literature. “Oral allergy syndrome” (SOA) is a type of food allergy caused by various flavors, food additives, nuts, fruits and vegetables. Typical symptom is itching in the oral cavity and throat, which occurs almost immediately after ingestion of food in the oral cavity, and lasts until the food is swallowed. A number of authors (18) indicate that the frequency of SOA is 5–8%; and conditions up to anaphylaxis occur in 1–2% of patients. Pollen from birch, ragweed and other herbs can also cause SOA, which occurs at any time of the year.

Food allergies affect up to 6% of young children, most of which “outgrow” sensitivity, and about 2% of the total population (19). Food allergic reactions cause various symptoms associated with the skin, the gastrointestinal tract and the respiratory tract, and may be associated with IgE-mediated and non-IgE-mediated response. The adaptive immune system of the mucous membrane is especially skilled in suppressing responses to non-hazardous antigens (oral tolerance) (20, 21).

Why did the pharynx, which is exposed to both respiratory and food allergens, fall out of the attention of modern science?

Based on the foregoing, we have developed a diagnostic algorithm for examining such patients.

The purpose of our work was to identify patients with an allergic form of chronic pharyngitis.

Material and methods

The retrospective study included 101 patients. We distinguished 3 groups of patients: group 1 - 35 patients with gastrointestinal diseases (reflux esophagitis); group 2 - 30 patients with psychosomatic disorders - determined by the psychosomatic questionnaire, the absence of local symptoms of inflammation; group 3 - 36 patients with the allergic nature of the disease.

In the first group, the following complaints were: sore throat and burning, unpleasant aftertaste in the mouth, choking, frequent heartburn. An allergic history is not burdened. There were no other complaints from the ENT organs. Seasonality of complaints is not observed. Some of these patients are examined and observed by gastroenterologists and have gastroesophageal reflux disease.

In the second group patients complained of feeling of a “lump” in the throat, sore, choking, which is

characteristic of chronic pharyngitis, as well as complaints of a lack of appetite, irritability, a feeling of anxiety, nervousness and panic, sleep disorders typical for patients with anxiety disorders and depressions.

In the third group patients had complaints of: sore throat, scratchiness in throat, burning, cough, sneezing, nasal congestion and nasal discharge, lacrimation. In some patients, complaints are seasonal. Some patients have perennial complaints, but have exacerbations in the spring-summer period, as well as the presence of allergic diseases in the family.

Results

We carefully collected a medical history of all patients. We used a questionnaire, which includes: an Anamnesis of current disease, family history, allergic anamnesis, the presence of complaints of chronic pharyngitis (Table 1). We also use a questionnaire that identifies the influence of the somatic status of the patient in the development of anxiety and depression, based on Generalized Anxiety Disorder 7-item (GAD-7) scale, The PHQ-9 (Patient Health Questionnaire-9) and the Hospital Anxiety and Depression Scale (HADS). All patients underwent clinical examination - pharyngoscopy, Laboratory and *instrumental methods* of diagnosis: complete blood count test (CBC), cytological examination of nasal and pharyngeal mucosal secretions; concentration of general and specific IgE of pharyngeal mucus on the cellular composition;

In the first group, in the picture of pharyngoscopy were symptoms of local inflammation. CBC test and cytological examination of the pharyngeal mucosal secretions included inflammatory changes. No pathological changes were observed in the nasocytogram. Reference values of total serum Ig E were within normal limits.

In the second group of patients, the local symptoms of inflammation were absent. The results of clinical laboratory and instrumental methods of diagnosis showed lack of signs of an inflammation. After analyzing and evaluating the results of test that identifies the influence of the somatic status of the patient in the development of anxiety and depression, subclinically or clinically the expressed depression was detected.

In the third group patients had local signs of inflammation while pharyngoscopy; leukocytosis in CBC test, an increased number of eosinophils.

Cytological examination of the nasal and pharyngeal mucus: an increased number of leukocytes, with eosinophils prevailing among leukocytes (more than 5%), an increase of total E.

Discussion

Suchwise, we highlighted the main complaints that are inherent in all forms of chronic pharyngitis: perspiration, pain, burning in the throat. However, other complaints may vary. Therefore, it is very important during the initial examination of such patients to use the diagnostic algorithm already at the stage of history taking.

We offer a diagnostic algorithm for chronic pharyngitis:

- 1) clinical examination;
- 2) a history taking:
 - anamnesis of life (bad habits, working conditions, contact with harmful substances);
 - medical history;
 - genetic history;
 - allergic history due to the time of occurrence of allergy manifestations (persistent or intermittent forms), comorbidity (AR, BA, allergic esophagitis, etc.);
 - the presence of chronic diseases of the gastrointestinal tract, especially reflux esophagitis;
 - the presence of psychogenic diseases (we use a questionnaire that identifies the influence of the somatic status of the patient in the development of anxiety and depression, based on Generalized Anxiety Disorder 7-item (GAD-7) scale, The PHQ-9 (Patient Health Questionnaire-9) and the Hospital Anxiety and Depression Scale (HADS));
- 3) cytological examination of nasal and pharyngeal mucosal secretions;
- 4) CBC test;
- 5) concentration of general and specific IgE of pharyngeal mucus on the cellular composition;
- 6) allergist consultation - identification of causally significant allergens (food and / or respiratory), the relationship with oral allergy, etc.

Conclusion

Chronic pharyngitis is a multidisciplinary problem that requires comprehensive study with the use of modern diagnostic capabilities. The allergic form of chronic pharyngitis is a local manifestation of a systemic allergic disease, is practically not detected and is not considered during statistical processing, masked under various other diagnoses, and, accordingly, is not treated with adequate anti-

allergic approaches and agents. This work is the first attempt to draw attention to the role of allergies in the pathogenesis of chronic inflammation of the pharynx. The use of a diagnostic algorithm at an early stage showed that 30% of patients with complaints of chronic pharyngitis have an allergic etiology of the disease. This group of patients requires further examination by an allergist.

Table1. Complaints specific to patients with chronic pharyngitis

Symptoms	I group of patients with concomitant gastrointestinal pathology	II group of patients with a violation of psychosomatic status	III group of patients with a burdened history and manifestations of allergies
Sore throat	+	+	+
Burning in throat	+	+	+
Scratchiness in throat	+	+	+
Cough			+
Sneezing			+
Feeling of a “lump” in the throat		+	+
Excessive tearing (lacrimation)			+
Nasal discharge			+
Nasal congestion			+
Breathlessness or a feeling of suffocation.		+	+
Pyrosis (Heartburn)	+		
Unpleasant aftertaste in the mouth	+		
Lack of appetite	+	+	
Choking	+	+	
Irritability and nervousness		+	
Sleep disorders		+	
Feeling of anxiety, and panic		+	

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Investigation of the effectiveness of tranexamic acid solution to optimize the control of perioperative bleeding during tonsillectomy

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Abstract

Recurrent tonsillitis is one of the most common ORL diseases. Tonsillectomy, as a method of surgical treatment associated with blood loss, and is accompanied by frequent perioperative bleeding. For the control of bleeding, it is advisable to use fibrinolysis inhibitors, one of which is tranexamic acid (TA). The study aimed to optimize the approach to performing tonsillectomy by preoperative application of a TA solution to reduce the volume of perioperative blood loss. Clinical studies were performed in 107 patients with recurrent tonsillitis who underwent bilateral tonsillectomy. The patients were divided into two groups. In the 1st (main) group of 54 patients in the preoperative period was administered a 10% solution of TA at the rate of 10 mg/kg body weight. The 2nd (control) group consisted of 53 patients without the use of TA. The efficacy of using tranexamic acid was evaluated by clinical (surgery time, the volume of blood loss intraoperatively, accounting for postoperative events, evaluation of the incidence of postoperative bleeding), and laboratory data (baseline and postoperative levels of D-dimer, level of soluble fibrin complexes. In group 1, a statistically significant decrease in the volume of blood loss, a decrease in the frequency of occurrence of intraoperative complications, postoperative bleeding, and a reduction in the triviality of the operation were determined. According to laboratory data, in patients of this group, the increase in the content of fibrin lysis products, the extension of thrombin time was significantly less pronounced than in the 2nd comparison group. The use of 10% TA solution before performing bilateral tonsillectomy leads to a decrease in blood loss, frequency, and the degree of occurrence of perioperative complications. Due to this, the duration of the operation of bilateral tonsillectomy is reduced.

Key words: recurrent tonsillitis, tonsillectomy, bleeding, tranexamic acid, D-dimer,

Introduction

The problem of recurrent tonsillitis (RT) remains relevant today, due to the frequency of pathology and its relationship with diseases of other organs and body systems (1). RT occupies a central place among diseases of the pharynx, being the most common pathology in the practice of an otorhinolaryngologist. The frequency of this disease is continuously growing and does not tend to decrease (2). According to recent studies, RT affects 15 - 20% of the adult population (3, 4). One of the treatment methods for RT is a tonsillectomy, one of the most common operations in otorhinolaryngology. In specialized departments of hospitals, the proportion of tonsillectomy reaches 20% of all surgical interventions (4). The main criteria for the safety of tonsillectomy are the frequency of intraoperative,

early and late postoperative complications, long-term results of treatment. Among all perioperative complications, tonsillectomy is most often accompanied by postoperative primary and secondary bleeding; their frequency varies from 0.1 to 8-10% (5). The best preventive measure to prevent postoperative bleeding is a reliable primary surgical hemostasis. However, especially in the event of secondary bleeding, it is advisable to use drug hemostatic therapy, which is an inhibitor of fibrinolysis, which includes tranexamic acid (6, 7, 8). TA is a synthetic derivative of the amino acid lysine, belongs to the group of antifibrinolytics, and is used as a hemostatic drug. The antifibrinolytic effect of tranexamic acid is to block the lysine binding sites in the plasminogen molecule.

This block, in turn, prevents the conversion of plasminogen to plasmin and prevents the connection of plasmin and tissue plasminogen activator with fibrin. As a result, fibrin degradation is suppressed. TA has a local and systemic hemostatic effect in bleeding associated with increased fibrinolysis activity. In addition to antifibrinolytic action, TA normalizes platelet function and capillary permeability.

TA is widely used to reduce blood loss during operations in cardiac surgery, orthopedics and traumatology, urological operations, and during cesarean section (9, 10, 11, 12, 13). The authors present clinical data that indicate a decrease in the volume of blood loss and the frequency of blood transfusion during surgical intervention with the use of a TA solution (14). At the same time, in some of the studies, there was no significant efficacy of using a solution of TA in tonsillectomy (15). In contrast, others confirmed a significant decrease in blood loss (16, 17). A systematic review and meta-analysis of the use of TA in tonsillectomy showed that most studies were conducted before 1980. Therefore, to study the risks and benefits of using a TA solution, it is necessary to perform a new, extensive, and well-planned randomized controlled trial (18).

The study aimed to optimize tonsillectomy surgery to reduce the volume of intraoperative blood loss, the frequency of intraoperative and postoperative complications, and to improve the course of the postoperative period in patients by preoperative use of a tranexamic acid solution.

Material and methods.

A comparative study was conducted at the Department of Otorhinolaryngology of Odessa National Medical University in Odessa City Clinical Hospital No. 11. Under the supervision were 107 patients with recurrent tonsillitis. Among the patients were men - 51 (48%) and women - 56 (52%). The average age of patients was 24.6 years. All patients underwent surgical treatment in the volume of bilateral tonsillectomy.

The conditions for inclusion in the study were: voluntary consent to participate in the study, the presence of recurrent tonsillitis, confirmed by the history and objective examination, the presence of indications for surgical intervention. The exclusion criteria were: age up to 18 years, pregnancy and lactation, acute infectious diseases, chronic

concomitant diseases in the stage of exacerbation or decompensation.

All patients were divided into two groups. The first group consisted of 54 patients operated on in the volume of bilateral tonsillectomy using endotracheal anesthesia. In the preoperative period, 30 minutes before the start of surgery, the patients were injected with 10% TA solution at a rate of 10 mg/kg body weight.

The second control group consisted of 53 patients operated on with the use of endotracheal anesthesia, who were not given TA in the preoperative period.

The groups were homogeneous by age, gender, and clinical course of the disease ($P > 0.05$). In the first group, there were 31 men (57%) and 23 women (43%), the median age was 24.5 years. In the second group, there were 28 men (53%) and 25 women (47%), the median age was 24.7 years. The disease in most patients has been observed for more than five years: 39 (72%) in the first group and 41 (77%) in the second. According to the doctor's appointment, 30% and 36% of patients in groups 1st and 2nd were treated, respectively. 39% and 26% of patients preferred self-medication, respectively.

The groups also did not differ significantly in the average number of exacerbations of recurrent tonsillitis in the anamnesis (Table 1). All patients underwent a comprehensive general clinical examination: a collection of complaints, and clarification of the medical history, standard examination of ORL organs. Laboratory and instrumental studies included a general analysis of blood and urine, a coagulogram, a blood test for sugar, a biochemical blood test, a blood group, a Rh-factor, a blood coagulation time, a D-dimer, a soluble fibrin-monomer complex (SFMC), and thrombin time. Additionally, an ECG, chest x-ray, and a blood test for syphilis were performed.

In the postoperative period, a daily medical examination of patients was performed. We took into account the presence of reactive phenomena in the oropharynx, such as edema, hyperemia, fibrinous deposits, the reaction of regional lymph nodes, and signs of ongoing bleeding. When evaluating the performed surgical intervention, the following indicators were taken into account: the volume of blood loss during the operation, the presence of episodes of bleeding during the operation that required coagulation or ligation of the vessels, flashing with a tampon, the presence of primary and secondary bleeding in the postoperative period, and the duration of the operation.

The effectiveness of TA use was evaluated according to clinical data (time of surgical intervention, intraoperative blood loss, assessment of the incidence of postoperative bleeding), and laboratory parameters (initial and postoperative level of D-dimer, SFMC level, thrombin time). The activation of fibrinolysis is accompanied by the cleavage of fibrin under the influence of the proteolytic action of plasmin, and the formation of degradation products of fibrin and fibrinogen, which interact with fibrin monomers, increasing the amount of SFMC. The specific product of the degradation of fibrin under the action of plasmin and other fibrinolytic is the D-dimer. Its concentration in the blood is proportional to the activity of fibrinolysis and the amount of fibrin subjected to lysis. The degradation products of fibrin and fibrinogen compete with thrombin and, thus, slow down the formation of clots, preventing the conversion of fibrinogen to fibrin. This process contributes to the extension of thrombin time, an indicator that marks the interval necessary for the conversion of fibrinogen to fibrin. We determined the level of D-dimer, the amount of SFMC, and the thrombin time in patients immediately before surgery and in the postoperative period.

Statistical data processing was performed using the programs for biomedical research, Microsoft Excel 2010, and Statistica 6.0 (StatSoft, 2006). The average values are given in the form ($M \pm m$), where M is the average value of the indicator, m is the standard error of the mean. The reliability of the differences was evaluated using Student's t-test. Statistical processing of data that did not correspond to the normal distribution was performed using non-parametric methods of statistical analysis according to the Mann-Whitney U test.

Results.

To assess the surgical intervention and the effectiveness of the use of TA, we conducted a comparative analysis of the duration of the operation in different groups of patients. The average time of tonsillectomy in patients of group 2 was 43 min (from 32 to 50 min), and in group 1 - 37 min (from 30 to 48 min). The intergroup difference is statistically significant ($p < 0.01$), which confirms the shorter duration of the operation using a 10% solution of TA. The average volume of blood loss during tonsillectomy in group 1 was 82 ml (from 45 to 112 ml), and in group 2 it was 101 ml (from 53 to

147 ml). Thus, the volume of blood loss in 1st group of patients was significantly lower ($p < 0.01$) compared with 2nd group.

Intraoperative events were distributed as follows (Table 2). The need for vascular stitching arose in 13 patients: in 5 patients from the main group and in 8 patients from the control group. The need for stitching brackets with a cotton-gauze ball arose in 8 patients, three patients of the main group, and five patients from the control group. The need for additional administration of procoagulants was in 16 patients, among them six patients from the main group and ten patients from the control group. Primary bleeding was recorded in five patients of the 1st group and eight patients of the 2nd group. Secondary bleeding was observed in four patients, three patients from the control group, and one of the main.

Eleven hemorrhages of degree A1-A2 were recorded. In this case, there are no signs of ongoing bleeding, normal laboratory parameters are noted, and bloody saliva is anamnesticly noted. During the examination, a fibrin film or a blood clot is observed after the removal of which there is no bleeding. Such bleeding occurred in 4 patients from group 1 and in 7 patients from group 2. Four episodes of bleeding related to type B1, in which minimal bleeding is visualized, which stops after the use of an adrenaline-treated swab.

Of these, there were two patients from group 1 and two patients from group 2. Two cases of grade B2 bleeding were also noted when hemostasis using local anesthesia was necessary. Both of these cases occurred in patients from group 2. Bleeding related to class C and D was not recorded.

In the postoperative period, a statistically significant increase in the parameters of SFMC, D-dimer, and thrombin time occurred in patients of both groups.

However, in group 1, the increase in the content of fibrin lysis products and lengthening of thrombin time was significantly less pronounced than in group 2 (Table 3).

Based on the results obtained, it was found that the proposed method with the introduction of a 10% tranexamic acid solution in the preoperative period allows optimizing the operation of bilateral tonsillectomy.

Conclusions

1. The use of TA significantly reduces the duration of surgery for bilateral tonsillectomy. The average time to perform surgery in group 1 is 37 min versus 43 min in the control group, which is 6 min.
2. The use of TA significantly reduces the amount of blood loss during surgery. The average volume of blood loss in group 1 is 82 ml versus 101 ml in 2 control.
3. The use of TA helps to reduce the incidence of intraoperative complications.
4. The use of TA minimizes the incidence and degree of postoperative bleeding.

The authors declare no conflict of interest.

Informed consent was obtained from all patients included in this study.

Table 1 - The frequency of exacerbations of recurrent tonsillitis

Frequency of exacerbations	1 st group	2 nd group
Less than once a year	6 (11%)	7 (13%)
1-2 times a year	8 (15%)	6 (11%)
3-4 times a year	28 (52%)	31 (59%)
More than 4 times a year	12 (22%)	9 (17%)

Table 2 - Recording perioperative events

Indicators	1 st group	2 nd group
Need for flashing vessels	5	8
Need for firmware brackets with a cotton-gauze ball	3	5
The need for additional administration of procoagulants	6	10
Episodes of primary bleeding	5	8
Episodes of secondary bleeding	1	3

Table 3 - Laboratory parameters in groups of patients undergoing tonsillectomy surgery with and without the use of preoperative administration of 10% TA solution

Indicators	1 st group			2 nd group		
	Before surgery	After surgery	P ₁	Before surgery	After surgery	P ₂
D-dimer, mkg/ml	0.35± 0,13	0.70± 0,09	< 0,05	0.34± 0,19	1.61± 0,32	< 0,001
SFMC, mg/100 ml	4.2± 0,35	5.5± 0,27	< 0,05	4.1± 0,67	9.5± 1,35	< 0,001
Thrombin time, s	11,1± 0,27	12,1± 0,18	< 0,05	11,4± 0,43	15,1± 1,12	< 0,001

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Approaches to the stage-by-stage and complex treatment of children with dysplastic scoliosis of i - ii degrees

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Abstract

The problem of treating dysplastic scoliosis in children is very relevant. The significant prevalence of pathology and early disability of patients necessitates the development of new methods to increase the effectiveness of therapeutic approaches, especially at the initial stages of the pathological process. Important for treatment is the consideration of dysplastic scoliosis as a manifestation of mesenchymal insufficiency syndrome. Our study aimed was to create individual stage-by-stage rehabilitation programs for children with dysplastic scoliosis of the I-II degree, including methods of differentiated kinesiotherapy and electrotherapy. In our study, we analyzed the results of complex stage-by-stage approaches to the treatment of children from 7 to 16 years old with dysplastic scoliosis of the I-II degree. Treatment and rehabilitation complexes included climatotherapy, standard kinesiotherapy, electrotherapy, massage, and balneotherapy (sanatorium-resort stage), as well as combined kinesiotherapy at the outpatient stage. The use of staged and integrated approaches to the treatment of children with dysplastic scoliosis of the I-II degree increases the effectiveness of therapy. It improves the quality of life of this group of patients.

Key words: *scoliosis, children, treatment, electrotherapy, kinesiotherapy, connective tissue dysplasia,*

Introduction

Dysplastic scoliosis (DS) occupies a leading place in the structure of pediatric orthopedic pathology. The problem of diagnosis and treatment of DS in children is one of the critical problems in pediatrics and orthopedics, not only due to the significant prevalence of pathology but also because of the frequent complications with the development of severe deformities. The progressive nature of the course of the disease leads to the development of a scoliotic disease, early disability in 50 - 75% of cases (1, 2).

Connective tissue dysplasia (CTD) is a genetically determined condition characterized by defects in the fibrous structures and the primary substance of the connective tissue. They lead to disruption in the formation of organs and systems, have a progressive course, and determine the characteristics of the associated pathology. Undifferentiated CTD is a heterogeneous group of diseases, which, in turn, can lead to various chronic diseases with impaired morphology and function of internal organs (3, 4).

A variety of clinical manifestations characterizes CTD: from benign subclinical forms to multiple organ and polysystemic pathologies, often with a progressive course. CTD in children, being a multifactorial pathology, phenotypically manifests itself as numerous organ disorders, primarily from the cardiovascular and nervous systems, as well as the musculoskeletal system (5, 6).

Clinical and morphological manifestations of undifferentiated CTD may include various skeletal changes associated with a violation of the cartilage structure: disproportionately long limbs, arachnodactyly, chest deformities, spinal deformities, flat feet, pathology of tooth development, occlusion, joint pathology (7). Changes in the skin are also characteristic: hyperelasticity, thinning, a tendency to trauma, and the like. Also, CTD manifests various lesions of the cardiovascular system: prolapse of the heart valves, venous insufficiency, varicose disease, etc. Also, with a high frequency, there are changes in the

organs of the gastrointestinal tract, genitourinary, and bronchopulmonary systems (3, 5, 6).

DS, as a rule, is one of the manifestations of the connective tissue dysplasia syndrome, which, of course, requires consideration when compiling individual comprehensive programs for the rehabilitation treatment of this patient population.

The basic complex of treatment for children with DS consists of massage, physiotherapy, apparatus physiotherapy, and the like.

Physiotherapeutic methods are an essential component of integrated approaches in the treatment of DS. The goal of physiotherapy is to create physiological prerequisites for restoring the correct position of the body in space (training the strength endurance of the muscles of the trunk, the formation of the muscle corset), stabilizing the scoliotic process, and in the early stages, correcting the deformation. Today, the use of electric currents for therapeutic purposes is well known, and the high efficiency of their use is proved (8).

The most common electrotherapy for DS is electrical stimulation of the back muscles, which is usually carried out using sinusoidal modulated currents. However, the need for action on the contracted muscles is not always taken into account. Short pulse electroanalgesia (TENS therapy) has trophotropic, neurotropic, analgesic, and muscle relaxant effects (8, 9).

An integral component of the comprehensive treatment of such patients is kinesiotherapy, a method of rehabilitation therapy based on movement. Kinesiotherapy can affect both individual links in the pathogenesis of dysplastic pathology of the spine and the entire motor system as a whole (10, 11). The main tasks of kinesiotherapy are stabilization of the vertebral-motor segment, strengthening the muscle corset and accelerating the recovery processes in its structures, normalizing the tone of the paravertebral muscles, restoring healthy posture and fixing optimal motor stereotypes (12).

Adequate kinesiotherapy initiates the maturation of dysplastic tissues, leads to an improvement in the patient's motor activity and remodeling of the affected structure. Stimulation of the motor-visceral mechanism contributes to inhibition or elimination of pathological conditioned reflex connections, mobilization of compensatory functions, and the formation of functional compensation (13).

Recently, new options for kinesiotherapy have appeared that combine dosed unloading of the spine with simultaneous muscle training, for example, on

an inclined plane using the Evminov technique, which is essentially a combination kinesiotherapy. The main goal of CK is to stop the progression and correction of spinal deformity by achieving symmetry of the muscle corset and increasing muscle endurance (14). Today, there has been evidence of the promise of using balneotherapy in the complex treatment of disorders of the musculoskeletal system (15, 16).

A high risk of pathology progression, despite the variety of treatment methods, necessitates not only the use of new physical factors in complex treatment but also the creation of an effective stage-by-stage treatment system for this patient population.

The work aimed to increase the effectiveness of treatment of children with DS I-II degree through the use of complex staged treatment using differentiated approaches to electrotherapy and kinesiotherapy, taking into account the degree of undifferentiated connective tissue dysplasia.

Object and research methods

We examined 167 children aged 7 to 16 years with DS I - II degree. There were 64 boys (38.3%), girls - 103 (61.7%), of which primary school children - 79 (47.3%), and high school children - 88 (52.7%). DS of I degree was diagnosed in 123 (73.6%) patients; DS of II degree was diagnosed in 44 (26.3%) cases. Most of the children had a lumbar-deformity type of deformity - 96 (57.5%) cases, lumbar and thoracic type of DS - in 43 (25.7%) and 28 (16.8%) children, species-like. The severity of disorders in patients with DS of I degree was $(39.3 \pm 1.1)\%$, with DS of II degree - $(41.4 \pm 1.3)\%$.

All examined patients had manifestations of mesenchymal insufficiency. The most common were changes in the musculoskeletal system and the cardiovascular system. Dysplasia of the connective tissue of I degree was in 98 (58.7%) patients, II degree in 64 (38.3%) children, III degree in 5 (3.0%) cases.

All children underwent general clinical and orthopedic examination, the performance of functional tests, X-ray, electromyographic, and laboratory studies. We assessed the severity of disorders (SD), the overall treatment effectiveness (TE), and the coefficient of efficiency (CE) according to the integrated scale for assessing the orthopedic and functional state of children with scoliosis (17).

Children received complex and staged treatment, which included a sanatorium-resort (twice a year)

and outpatient (throughout the year) stages. At the sanatorium stage, treatment and rehabilitation complexes (TRC) were used, which included: orthopedic regimen, climatotherapy, kinesiotherapy and electrotherapy, balneotherapy (sodium chloride baths (SCB)), massage.

Depending on the type of TRC, we used standard and combined kinesiotherapy. Standard kinesiotherapy (SKT) consisted of a set of exercises to strengthen the muscle corset, the formation of the correct body position in space, and the correction of spinal deformity. The duration of one lesson was 30-40 minutes.

Combined kinesiotherapy (CKT) was carried out according to the Evminov technique, on an inclined plane, the duration of one lesson was 20-30 minutes. Exercises CKT was used in the form of complexes for the chest, thoracolumbar, and lumbar types of DS.

We selected kinesiotherapy programs depending on the age of the child, the degree and type of pathological disorders, concomitant pathology, and the level of physical development of the patient.

Electromyostimulation was performed using sinusoidal modulated currents (SMC) on an Amplipulse 5 apparatus with the following parameters: modulation depth - 75%, frequency 80 Hz, current strength — until light vibration was felt, electrode localization — paravertebral at the level of the apex of the curved arc of the convex side. The duration of the procedure for children 7-11 years old was 10 minutes, 12-16 years - 12 minutes, per course - 10 procedures daily.

Short pulse currents (TENS therapy) were performed paravertebrally at the level of the apex of the concave side curvature arc. The duration of the procedure was for children 7-11 years old - 12 minutes, for children 12-16 years old - 15 minutes, a course of 10 procedures daily. In those complexes in which alternation (every other day) of electrical stimulation and TENS therapy was used, electrotherapy was carried out by a general course of 10 procedures (SMC - 5 procedures and TENS therapy - 5 procedures).

Therapeutic massage of the muscles of the back and abdomen was performed according to generally accepted rules, taking into account the age of the child. The duration of the procedure was 10 - 20 minutes., On the course - 15 - 20 daily procedures.

Patients also received sodium chloride baths (SCB) with a concentration of sodium chloride of 20 g / l, water temperature - 36 - 37 ° C. The duration of the

procedure for children 7-11 years old was 10 minutes, for children 12-16 years old - 12 minutes, in a day, on a course - 10 procedures.

Climatotherapy included walking to the sea in the morning and evening (marine dosed aerotherapy), for 1 to 2 hours.

All children received individual correction following the degree of pathological disorders.

All patients were divided into two groups. The first group consisted of 53 children who received kinesiotherapy as monotherapy, and depending on its type, were divided into two subgroups: 1a subgroup consisted of 26 children who received SKT, 1b subgroup - 27 children who received CKT. Patients of the second group (114 children) who received TRC at the spa stage and kinesiotherapy at the outpatient clinic were divided into four subgroups. Subgroup 2a included 27 children who had TRC No. 1 (climatotherapy, SCB, massage, SKT, and electromyostimulation); subgroup 2b included 28 patients who received TRC No. 2 (CTK was used instead of SKT); subgroup 2c comprised 29 children who received TRC No. 3 (additionally TENS therapy), and the 2d group included 30 patients who received TRC No. 4 (electrotherapy with alternating, every other day, effects on the back muscles - electromyostimulation and TENS therapy).

Results and discussion.

After a course of kinesiotherapy as monotherapy at the outpatient stage, in both subgroups of patients of the first group, functional tests improved. In children of subgroup 1b who received CKT, indicators of the functional state of the cardiovascular and respiratory systems were better than in patients of subgroup 1a. Indicators of strength endurance of the muscles of the back and abdomen in subgroup 1b each increased 1.7 times, while in patients 1a of the subgroup, the increase occurred only 1.2 and 1.3 times ($p < 0.05$). SD in patients of subgroup 1b decreased by 12.8%, while in children of subgroup 1a this indicator reduced by 9.4% ($p < 0.001$), and the total TE was $(33.1 \pm 1.3)\%$, which is 5.7% ($p < 0.01$) more than after application of SKT.

All children of the second group had improved orthopedic status and functional tests. However, in patients in the 2c subgroup, the strength endurance of the back muscles increased 1.8 times, the abdomen - 1.7 times ($p < 0.05$), whereas in children of subgroup 2a these data increased, respectively, by 1.4 and 1.3 times ($p < 0.05$).

The SD after the course in the 2b and 2c subgroups decreased by 13.8 and 13.5%, respectively, while in patients of the 2a subgroup - by 11.7% ($p < 0.001$). TE in children of subgroups 2b and 2c was ($33.8 \pm 1.8\%$) and ($34.2 \pm 2.2\%$), and in patients of subgroup 2a it was ($30.9 \pm 2.1\%$) ($p < 0.05$). In the 2d group, the results of using TRC No. 4 were significantly better. The SD index in children of the 2d subgroup decreased by 20.3% compared with the data before treatment and amounted to ($21.3 \pm 1.1\%$) ($p < 0.001$), the CE index increased by 26.5% compared with the 2a subgroup ($p < 0.01$), the TE index was 21.4% higher compared to subgroup 2a and amounted to ($52.3 \pm 1.3\%$) ($p < 0.05$) (Table 1). An analysis of the long-term results of treatment of patients of the first group showed that the number of good results when using kinesiotherapy as monotherapy was 37.1%, satisfactory 42.9%, and unsatisfactory 20.0%. In patients of the second group, the best results were achieved in subgroup 2d (CKT at the outpatient stage, TRC No. 4 at the sanatorium stage). The number of good long-term results was 84.6%, satisfactory - 11.5%, unsatisfactory - 3.9%. In children of subgroup 2a (standard kinesiotherapy at the outpatient stage, TRC No. 1 at the sanatorium stage), the results were as follows: good - 45.5%, satisfactory - 31.9%, unsatisfactory - 22.7%. In subgroups 2b and 2c, the treatment results did not significantly differ, although they were significantly better than in subgroup 2a and significantly worse compared to subgroup 2d ($p < 0.05$). Thus, the analysis of the obtained data showed the advantages of using CKT not only as monotherapy, but also as a component of TRC at the sanatorium-resort stage of treatment, which was manifested in an improvement in the functional parameters of the cardiovascular, respiratory and muscle systems,

stabilometric indicators, a decrease in SD, and an increase in ET.

As for electrotherapy, the obtained results testified to the effectiveness of differentiated bilateral electrotherapy (TENS therapy and electromyostimulation), which contributed to the symmetrization of paravertebral muscle tone.

We consider it possible to recommend the developed system of staged differentiated use of kinesiotherapy and electrotherapy for practical purposes in children with DS I - II degree. It is advisable to use CKT at the outpatient stage, and at the sanatorium-resort stage - TRC with the inclusion of CKT and electrotherapy.

Conclusions.

1. The use of kinesiotherapy in children with DS I-II degree in the form of combined kinesiotherapy at the outpatient stage, and as part of TRC at the sanatorium-resort stage, significantly increases the effectiveness of treatment of this group of patients.
2. Differentiated electrotherapy (TENS-therapy and electromyostimulation) as part of TRC at the sanatorium-resort stage of treatment of children with DS of the I-II degree, allows to halve the severity of pathological disorders and increase the effectiveness of treatment.
3. The introduction of a system of staged differentiated use of kinesiotherapy and electrotherapy in children with grade I - II DS provides good long-term results in 84.6% of patients.
4. A comprehensive assessment of the degree of CTD and the correction of these pathological disorders is an essential component in the formation of individual rehabilitation programs in children with DS of the I - II degree.

Table 1. The results of the use of TRC in patients of the second group, ($M \pm m$)

Indicators		Subgroups			
		2a (n=27)	2b (n=28)	2c (n=29)	2d (n=30)
SD, %	Before TRC	40,9±2,1	41,5±1,4	39,3±1,4	41,7±1,6
	After TRC	29,2±1,3**	27,7±1,1**	25,8±1,2**	21,3±1,1* **
CE		1,36±0,1	1,43±0,1	1,48±0,1*	1,72±0,1*
TE, %		30,9±2,1	33,8±1,8	34,2±2,2	52,3±1,3*

Notes:

1. * - $P < 0.05$ compared to the 2nd subgroup
2. ** - $P < 0.001$ compared to SD before TRC

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Management of temporomandibular disorders with ultrasound therapy and transcutaneous electrical nerve stimulation – a literature up-date

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Abstract

Introduction. Temporomandibular disorders are considered to have a multifactorial etiology; thereby different treatment modalities are available, from occlusal equilibration, medication and physical therapy. Among physical therapies, occlusal splints, low-level laser therapy, acupuncture, ultrasound, TENS frequently used in current practice. The aim of physical therapies is to re-establish the muscle physiology by increasing the local blood and lymphatic flow. The aim of this study was to provide some clinical guidance regarding ultrasound therapy and TENS in case of temporomandibular disorders. **Material and methods.** A research of literature has been performed - articles published over the last 10 years (January 2009 until December 2019) were searched by introducing a combination of different terms, using the Pubmed and Science Direct databases. **Results and discussion.** A total number of 611 articles were found. After applying the inclusion and exclusion criteria, 20 articles were taken into consideration for the present study. **Conclusion.** Based on the findings within this literature review it can be concluded that for patients suffering from TMDs, ultrasound therapy and transcutaneous electrical nerve stimulation represent an effective non-drug-based conservative option, in order to improve symptoms like pain or hyperactivity of the masticatory muscles. Because it was difficult to compare the studies included, as they do not offer an optimal usage (program, duration of sessions, or number of sessions) of each technique we consider that further randomized controlled clinical studies are necessarily to compare each physical technique as well their combined effect in case of patients with temporomandibular disorders.

Key words: TMD, ultrasound therapy, TENS,

Introduction

Temporomandibular disorder (TMD) is defined by the American Academy of Orofacial Pain as “a collective term which includes a number of clinical problems that involves the masticatory muscles, the temporomandibular joint (TMJ) and associated structures”. Among the most common signs and symptoms in TMDs there is limiting of mouth opening because of pain, TMJ sounds, and asymmetrical jaw movements (1,2).

As TMD's etiology is considered to be multifactorial, different treatment modalities are available, including occlusal equilibration, medication, and physical therapy. Physical therapies refer to several treatment options such as occlusal splints, low-level laser therapy, acupuncture, ultrasound, TENS, etc. The aim of physical therapies is to re-establish the muscle physiology by increasing the local blood and lymphatic flow (3).

Definition of ultrasound is “sound wave oscillating at a frequency greater than 20000 cycles per second”(4). The medical use for ultrasound therapy (US Th) started to be analyzed in the 1930s as it was

said to speed up the healing process and increase the quality of tissue repair (5). Currently this therapy is mainly used for muscle pain (6,7). US Th is known to reduce pain, increase joint mobility, accelerate the healing processes, increase the extensibility of collagen fibers, reduce muscle spasms (therefore a better mouth opening)(6).

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive, non-medicated, treatment option used for pain management in different musculoskeletal pathologies, including for TMDs (8, 9). It is considered that TENS's may activate the endogenous opioids system with an impact on the central inhibition, as the technique involves the application of an electrical stimulus on the major nerves (10,11).

The use of physical therapy in case of TMDs is controversial, as some articles are suggesting that their effect on pain is minimal (12). *The aim* of this study was to provide some clinical guidance regarding ultrasound therapy and TENS in case of temporomandibular disorders.

Methods

In order to find relevant and adequate articles for this literature review, an automated search of PubMed and Science Direct databases was conducted from January 2009 and up to December 2019. A combination of these following keywords was used: “temporomandibular disorder”, “TMD”, “temporomandibular joint disorder”, “TMJ disorder”, “TM disorder”, “ultrasound”, “ultrasonography”, “sonography”, „TENS”, “Transcutaneous Electrical Nerve Stimulation”. Before initiating the search, we took into consideration the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (13,14,15).

The following types of articles were *included*: 1. randomized clinical trials (involving patients with TMD), 2. systematic reviews and meta-analysis studies in which either ultrasound or TENS therapies were the treatment option for temporomandibular joint disorder (TMD) and 3. articles written in English. *Exclusion* criteria were as follows: abstracts that did not report data on the findings, articles written in other languages than English and studies performed on patients with systemic diseases or pain not related to TMJ.

Results

A total number of 611 articles were found. After applying the inclusion and exclusion criteria, 20 articles were taken into consideration for the present study.

Discussion

The aim of this study was to provide an up-date of literature regarding the use of physical therapy (ultrasound and TENS) in case of temporomandibular disorders. Thereby, the authors analyzed the articles included in this research and organized the findings based on topic and based on answering on some focus questions for each type of physical therapy.

a. What is the mechanism of action for each physical therapy?

Ultrasound therapy acts by the principle of a mechanical energy at increased frequency that stimulates tissue with sound waves that are beyond the upper limit of what the human ear can hear (4).

TENS involves the action of an electrical stimulus on the major nerves, as a neurophysiological mechanism is produced, depending on the parameters used (duration and amplitude). In clinical practice, there are two types of TENS – low frequency (LF, <5 Hz frequency of stimulation) and

high frequency (HF, >100Hz). There is also a ultra low frequency stimulation TENS (ULF) (<4Hz of frequency). A conventional TENS stimulator device will be able to transmit different ranges of frequencies, for both LF and HF TENS therapies (11).

When a patient receives HF-TENS therapy, the sensations are sometimes perceived as pleasant, or the subject does not feel anything. It is considered that HF-TENS analgesia appears rapidly, but can quickly stop once the stimulation is suspended (11).

On the other hand, the LF-TENS stimulation will determine analgesia after 20-45 minutes of administration, but the analgesic effect will last longer after the stimulation is suspended. Also, the LF-TENS must be administrated to such amplitude so it will feel uncomfortable for the patient (11).

Neuromuscular TENS is also known as ultra low-frequency TENS (ULF-TENS) and it will act as an exciter for the motor fibers of the facial nerve, which will lead to a relaxation of the masticatory muscles. The practitioner using this technique will achieve this way a physiological rest position of the jaw (11).

The effects of ultrasound therapy and TENS are resumed in Table 1.

b. What are the indications and contraindications?

US Th can be used to reduce pain, to increase joint mobility, to accelerate the healing processes, to increase the extensibility of collagen fibers and to reduce muscle spasms (therefore a better mouth opening)(4).

In case of temporomandibular disorders, ultrasound therapy is indicated in order to reduce the muscular activity of masticatory muscles. This therapy produces low-amplitude, low-frequency stimulus which will induce vibrations. When applied bilaterally those vibrations are able to reach some superficial divisions of the facial nerve as well as the mandibular division of the trigeminal nerve(18).

In dentistry, TENS has two major indications. The first indication is when the patient is suffering from musculoskeletal pain, like the pain in temporomandibular disorders; in those cases an antalgic TENS can be used to reduce pain. The second indication is for neuromuscular TENS, which is also used as a therapeutical strategy; as it produces a contraction of the muscle(s), neuromuscular TENS can be used by practitioners to conduct the mandible in Central Relation (10,11).

Monaco et al. also conducted a study in 2016, suggesting that ULF- TENS therapy might be able to

reduce the values of heart rate and breathing rate under acute mental stress conditions. The results of their preliminary study suggest that the analgesic effect obtained after TENS therapy might be induced by other mechanisms, such as an increase in parasympathetic tone associated with a decrease in the orthosympathetic tone, which leads to lower values for heart and breathing rate. (19).

US Th is contraindicated in some situations like infections, malignancy, bone fracture, cardiac pacemaker or other implantable devices, coagulopathies, untreated blood hypertension, pregnancy (20).

There are also situations when TENS therapy is not indicated, like patients having pace-maker or any other electrical device, in case of venous or arterial thrombosis or thrombophlebitis, patients with severe psychiatric disorders (dementia, Alzheimer's disease), and in case of pregnant patients(8,21,22).

c. What are the protocols for using US Th and TENS?

The protocols of using both physical therapies differ between the studies included in this review. Table 2 resumes the protocols found in the clinical studies considered in this study.

d. What results can be obtained after using US or TENS therapy?

It is known that in case of ultrasound therapy, a small amount of the sound waves reach the profound muscles as well as the TMJ(12). In this context, Haseeb et al. reported that US Th might be able to reach even the trapezoid muscle (7).

Panhoca et al. performed a clinical study, testing the efficiency of a combination treatment - US Th and photobiomodulation Th (PBMT)- on 13 patients (ages between 23 and 66; all suffering from TMD). The results showed that the patients' quality of life has improved, and the therapy effects were still lasting one month after the end of the treatment(6).

Hussain et al. compared US Th to sham US Th on 20 female subjects with bilateral masseter myalgia. Ultrasound therapy produced an immediate increase in the pressure pain thresholds for the masseter muscles (which is considered a therapeutic effect), and an increase in intraoral temperature on subjects treated with US. Also, their results suggest that therapeutic ultrasound may be more effective than sham ultrasound for patients suffering from bilateral masseter myalgia(7).

Ramakrishnan and Aswath conducted a clinical study in 2017, on 50 patients suffering from temporomandibular disorders. The patients were

divided in 2 groups and they received US therapy – for first group an acoustic gel without pharmacological agents was used and for the second group a gel containing aceclofenac was used (the technique is called phonophoresis). The results have been analyzed with the help of a visual analogue scale (VAS) and by immunoturbidometry (measures the C reactive protein = CRP). The authors concluded that both therapies were efficient in reducing pain (VAS) and inflammation (CRP); also, phonophoresis was slightly superior compared to US Th, but no significant difference between the two therapies was obtained(17).

Overall, ultrasound therapy seems to be more effective as an adjunct to other therapies, than used alone (16) Khairnaret al. compared US Th with low-level laser therapy (LLLT), on 42 patients with TMD, distributed in 2 groups. All patients received non-steroidal anti-inflammatory drugs (Myospaz Forte) twice a day, 5 days preceding the treatment. Both methods have had good results reducing pain (VAS) and mouth opening, yet LLLT's results were considered superior in both cases (2). The beneficial effect of LLLT on patients suffering from temporomandibular disorders is also confirmed by other clinical studies (24). When Us Th and TENS were compared, researchers found that both of them were able to determine a significant thickness reduction of the masseter muscle. While both therapies were found to be effective on pain reduction, their results showed that US therapy is more effective compared to TENS (11,16).

Regarding the use of TENS in TMDs, in 2013, Monaco et al. conducted a clinical study studying the effects of sensory and motor TENS therapy on masticatory muscles. They demonstrated that the application of TENS is effective in reducing the activity of the masticatory muscles, as well in increasing the interocclusal distance, for patients suffering of temporomandibular disorders (25).

Cesar et al. studied the use of TENS therapy on 40 patients suffering from TMD. They concluded that short-term TENS therapy (a total of 50 minutes, using variations of low and high frequencies) reduces deep pain sensitivity and improves masticatory muscles activity (measured on electromyography)(26).

We also found a systematic review which does not support the use of ultrasound therapy, or TENS, as there are insufficient clinical data regarding their use (12).

Conclusion

Based on the findings within this literature review it can be concluded that for patients suffering from TMDs, ultrasound therapy and transcutaneous electrical nerve stimulation represent an effective non-drug-based conservative option, in order to improve symptoms like pain or hyperactivity of the masticatory muscles.

Nevertheless, it was difficult to compare the studies included, as they do not offer an optimal usage (program, duration of sessions, or number of sessions) of each technique. Because of lack of possible conclusion, we consider that further randomized controlled clinical studies are necessarily to compare each physical technique as well their combined effect in case of patients with temporomandibular disorders.

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Table 1 – Mechanism of actions for Us Th and TENS

ULTRASOUND THERAPY	TENS THERAPY
<p>US therapy is considered to be effective from both thermal (at a continuous frequency - 100% duty cycle) and non-thermal (at a pulsed frequency - 50% duty cycle) mechanisms (2,4,7).</p> <p>The acoustic energy that penetrates the soft tissue causes molecules to vibrate under repeated cycles of compression and refraction. If the intensity is increased, the frictional heat will also increase (2).</p> <p>Thermal US, at a depth of 8 cm, increases the temperature by 4 to 5 degrees Celsius, at 1.5 w/cm² or higher. At 1.25 w/cm² sound waves already cause tissue vibration (2).</p> <p>The cell metabolism and the cell permeability (which is altered to sodium in such a way that modifies the nerve conduction or the pain threshold) are directly influenced by the increase in temperature(16,17). The increase in temperature draws blood with oxygen, nutrients and removes inflammatory exudates. US prompts the de-granulation of mast cells, which release arachidonic acid (a precursor for the synthesis of prostaglandins and leukotriene)(2). The resolution of inflammation comes along with the reduction of pain(2).</p>	<p>Patil et al. resumed the three major theories by which TENS is considered to work (3):</p> <ul style="list-style-type: none"> - first theory suggests that TENS stimulates the thick sensory fibers (or A-fibers), which will block the thin C-fibers (pain-modulating fibers); as a result, the gate of pain signals (at the entry into the spinal cord) is closed, and an analgesic result is obtained; - another mechanism by which TENS is believed to act, is the release of some endogenous morphine-like substances, with analgesic properties; - a third theory suggests that TENS causes mild, rhythmic muscle contractions which increase blood and lymph flow, reducing the interstitial oedema, as well as reducing the amount of noxious tissue metabolites.

Table 2 – Suggested clinical protocol for US Th and TENS

US TH	TENS
<p>Khairnar et al. used a Bionics Innovation Unit at a frequency of 1 MHz and wavelength of 1.5 mm, 1.8 w/cm square for 10 minutes per session, with a coupling agent during therapy(2).</p> <p>Another study used Ultrasound Sonicator 740 device at 0.4 w/cm square with 100% duty cycle for 5 minutes, with acoustic gel pre-heated to 24 degrees Celsius (7).</p> <p>Panhoca et al. recommends using US Th for 2 sessions per week, for 4 weeks at a frequency of 1.0 MHz, 1 w/cm square, 50% pulsed work cycle, effective radiation area of 1.6 cm square. For better sound wave transmission an acoustic gel based on water can be used, and gentle, slow circular movements should be performed for 120 seconds (6).</p> <p>Shalu Rai used the US Th for 12 weeks, 3 times every 2 weeks(16) and Ramakrishnan et al. in his comparison used US Th 3 times a week, for 2 weeks at a frequency of 1MHz, intensity 1.5 w/cm square for 8 minutes(17).</p>	<p>Patil et al. used TENS therapy for a duration of 6 days, for approximately 30 minutes per session. The frequency of the electric current ranged between 10 to 40Hz, with an amplitude between 1 to 5 μA(3).</p> <p>For ULF-TENS therapy, it is indicated to use a Myomonitor TENS Unit which will generate repetitive, synchronous and bilateral stimulus at 1.5 seconds intervals, with an amplitude between 0-24mA, for 500μseconds, a 0.66Hz of frequency. The electrodes should be positioned on the jaw (anterior to the tragus), and another electrode, placed posterior, on the midline of the neck, lower than the hairline. For this protocol, ULF-TENS should be applied for a duration of maximum 60 minutes in order to assure masticatory muscular relaxation (22).</p>

The Ki-67 immunohistochemical expression of colorectal polyps

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Abstract

Background and objective: The chosen study mainly investigates the importance of immunohistochemical expression of Ki-67 in Colorectal polyps which are considered intraepithelial neoplasms and can be found in diverse dimensions from small polyps to large ones. During the examination process, dysplasia was observed in all polyps examined in the Ki-67 proliferation index. The study will clarify also their relationship to the size, dysplasia, and location of the polyps. Malignancy of the polyps with high and low dysplasia is far more expected. The idea of the development of colorectal cancer from previously existing adenomas has been widely spread based on epidemiological, clinical, postmortem and molecular biological studies. The significance of cell proliferation in the change of adenomatous polyps into colorectal cancer is incontestable, which is considered an axiom. The Ki-67 protein is another immunohistochemical marker applied for the identification of proliferative cells. So that there is a significant relationship between the type of adenoma and the Ki-67 expression, and three of the polyps in the Ki-67 expression were considered dysplasia.

Methods: Between the period of 2011 and 2016, 100 patients, (out of 40 were women and 60 of them were men) with endoscopic polypectomy were retrospectively analyzed at the Endoscopy Department of the Central Customs Hospital. Immuno-histochemically Ki-67 expressive polyps were performed in eight patients involved in the study group. The Ki-67 response was conducted via the monoclonal reflection bodies. (Leica Bond-Max automated immune stainer apparatus) The percentage of positively charged cells was recorded as Ki-67 labeling index (Ki-67-LI) and each painted nuclear was considered positive.

Results: The retrospective study included 100 paraffin blocks of polypectomized specimens. According to the histological examination of Hematoxylin and Eosin stained (H&E) preparations, there were 45 tubes, 23 tubulovillous, 16 inflammatory, 13 hyperplastic, 2 serrated and one polyp in the villous form were detected. The mid-aged patients were 56.78 ± 1.64 . Most of the patients around 38 patients in this study constituted 50 to 69 age groups and five patients were included between 40 to 49 age groups. The gender distribution of the cases was determined in 60 of males, 40 of females. Dysplasia was observed in all polyps examined in Ki-67 proliferation index. There is a significant relationship between the type of adenoma and the Ki-67 expression, and three of the polyps in the Ki-67 expression were considered dysplasia.

Conclusions: The study revealed that the Ki-67 immunohistochemical expression is significantly related to the size and the degree of dysplasia in colorectal adenomas, but does not have a significant relationship with the sex, age, and the type colorectal adenomas.

Key words: *colorectal adenoma, colorectal polyps, colon polyps, dysplasia, Ki-67 expression,*

Introduction

Colorectal polyps are intraepithelial neoplasms growing through from the wall of the colon and rectum to its origin can be found in different sizes ranging from small polyps to large ones. Generally, colon polyps are more founded pathology and commonly seen over 50 aged patients and are not only the malignant pathology but more the precursor of malignant neoplasms, where the polyps have a high likelihood of cancer. Cancer normally develops in around 5% of adenomatous polyps. (1,2)

Colorectal adenomas are more commonly observed in the developed Western states. Therefore, nutritional factors, environment, inflammatory diseases of the gastrointestinal tract, ulcerative

colitis, and Crohn's disease play an essential role in the formation of colorectal polyps. (3,4) Thus, the reduction of proliferation and apoptosis in colon cells increases the risk of carcinogenesis within the background of inflammatory diseases. Colorectal adenomas are mainly accompanied by epithelial dysplasia and as the main cause of malignant neoplasms, are "sneak" lesions of colon (intestinal) cancer, which plays a major role in the spread of colorectal polyps, and the formation of malignant neoplasms. (5,6) The adenomatous polyps are the crucially important cause of colorectal cancer. (7) Because of the fact that possibility of being cancer is higher in patients with adenomatous polyps.

Colon cancers encompass 30% to 50% of adenomas. The process of colorectal adenomas' transition to cancer is considered to be whether "seated" tumor, particularly "unformed" crypts located in the left hemi-colon, "toothed" tumor including crypts until basal layer or polyp-similar tumors consisted of ectopic crypts. (8,9,10)

The formation of ectopic crypts results in dysplasia. Abnormal differentiation of crypts in the basal layer leads to the development of colorectal cancer. (10) So that the colorectal polyps are considered in different sizes, ranging from small to large-sized polyps, even to pedunculated ones. Histologically, polyp cancers include normal epithelium, adenomatous tissue, atypia, and invasive invasion. So that the bigger polyps have a higher possibility of being cancer.

Polyps less than (<) 1 cm in size constitute 1% likely to be malignant, slightly greater than (>) 1 cm, around 1 to 2 cm of those have a 10% chance of becoming malignant, but those are 2 cm or greater (>) have a 40% chance of transforming into malignancy. However, in villous adenomas, polyps less than (<) 1 cm and 1 to 2 cm have a 10%, and more than 2 cm have a 53% chance of becoming malignant. So that these derivatives can be repeated and the risk of transition to the neoplastic process can be variable depending on their characteristics. (multiplicity, dimensions, histological structure, and dysplasia) It has been considered that 15% of all derivatives with a size of more than 1 cm are likely to be transmitted to malignant neoplasms within 10 years. (2,10)

The significance of cell proliferation in the change of adenomatous polyps into colorectal cancer is incontestable, which is considered an axiom. The Ki-67 protein is another immunohistochemical marker applied for the identification of proliferative cells. It is expressed in all phases of the cellular cycle, except the G0 phase. Thus, Ki-67 is both a nuclear and a nucleolus protein. (10) Contrary to many other cell cycle-associated proteins like PCNA (Proliferating Cell Nuclear Antigen), the Ki-67 antigen is consistently absent in inactive cells and is not detectable during the DNA repair processes. Consequently, the presence of Ki-67 antigen is strictly related to the cell cycle, which is restrained to the nucleus by signifying an important role of this structure in the maintenance or regulation of the cell cycle. (11)

The monoclonal antibody Ki-67 has the particular feature of recognizing. In this case, Ki-67 is the key marker of cellular proliferation sensitivity,

participating in cell proliferation as both a nuclear and a nucleolus protein. (3) Ki-67 proteins are present in all active phases of the cell cycle (G1, S, G2, and mitosis) but are not found in inactivated cells, and not in the process of DNT reparation. Thus, the Ki-67 antigen is seriously associated with the cell chain and is restricted to the nucleus showing that this structure plays a significant role in maintaining and/or regulating the cell cycle. A number of studies have shown that the clinical evaluation of the Ki-67 immuno-histochemical expression is important and there is no relationship between dysplasia and immunoreactivity of the Ki-67 expression. (5,6)

The study was conducted in order to assess the importance of the Ki-67 expression as an immunohistochemical marker for the early detection of the malignant changes in various colorectal adenomas. Hence, the chosen research is also aimed at evaluating the relationship between this marker and the different clinical-pathological parameters. (Including dysplasia of adenomas, location, type, size of the polyps). The aim of the study is to analyze the Ki-67 expression in the colorectal polyps and to clarify their relationship to the size, dysplasia, and location of the polyps.

Methods

Between the period of 2011 and 2016, 100 patients, (out of 40 were women and 60 of them were men) with endoscopic polypectomy were retrospectively analyzed at the Endoscopy Department of the Central Customs Hospital. The colonoscopy examination was performed in patients with complaints of gastrointestinal disorders, bleeding, bloody mucosal excretion, constipation, and at the same time, more than 45 aged people applied for screening purposes. The day before, the intestinal bowel preparation was done, and the cardiology consultation was requested for those with heart problems. The polyps detected during the investigation were interrupted depending on their sizes. So that the small polyps of less than 0.5 cm were taken out through the forceps biopsy and the large polyps were taken into the squeezed circle and then were eliminated. The tissue preparation was examined in the Central Customs Hospital Patomorphology Department. As a result, sections were taken from the paraffin embedded tissues by using microtome. All polyps detected amid the examination were sent to the pathological investigation. Pursuant to the pathohistologic

examination, there were 45 tubes, 23 tubulovillous, 16 inflammatory, 13 hyperplastic, 2 serrated and one polyp in the villous form were detected. Initially, all polyps were evaluated with Hematoxylin and Eosin stain. (H&E stain) At this time, the injured drugs were removed out from the investigation group.

Immunohistochemically Ki-67 expressive polyps were performed in eight patients involved in the study group. The Ki-67 response was carried out via the monoclonal reflection bodies. (Leica Bond-Max automated immunostainer apparatus) The percentage of positively charged cells was recorded as the Ki-67 labeling index (Ki-67-LI). As a result, each painted nuclear was considered positive.

Results

This retrospective study included 100 paraffin blocks of polypectomized specimens. According to the histological examination of Hematoxylin and Eosin stained (H&E) preparations, there were 45 tubes, 23 tubulovillous, 16 inflammatory, 13 hyperplastic, 2 serrated and one polyp in the villous form were detected. The middle age of the patients was 56.78 ± 1.64 . Most of the patients around 38 patients in this study constituted 50 to 69 age group and 5 patients were included between 40 and 49 age group. The gender distribution of the cases was determined in 60 of males, 40 of females

Generally, the proportion of the detection of colorectal adenomas in men and women is about 1.5:1. As for the localization of colorectal adenomas, the distal region of the colon was superior to the proximal region. The average size of the colorectal adenomas was $1.27 \text{ cm} \pm 0.11$, which ranged from 0.3 to 3.2 cm. The average size of the villous adenomas was 1.14 cm. The size of the tubular adenomas ranged from 0.8 to 3 cm, with an average of 1.38 cm. Tubulovillous adenomas range from 0.3 to 3.2 cm, with an average of 1.4 cm.

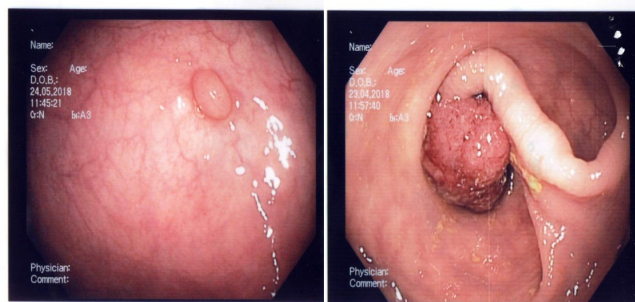


Figure 1. The presence of colorectal polyps during their colonoscopic examination

When the cases were inspected in terms of having or not having dysplasia, it was detected that dysplasia was present in 42 cases and dysplasia was absent in 58 cases. When 42 cases with dysplasia were followed, 26 cases constituting 61.9 % of it proceeded to the malignancy over time. 16 cases estimating 38.1 % of it did not develop the malignancy. Malignancy of the polyps with high and low dysplasia is far more expected. Dysplasia has been detected in large dimensional polyps, which overlaps with the literature data. In this manner, in the chosen study, there is 32.5% of dysplasia in polyps less than 1 cm, and polyps 1 to 3 cm have 70.58% of dysplasia, and 100% of dysplasia is observed in 3 cm large polyps. Dysplasia was detected 26 (32.5%) of 80 patients, which have smaller polyps of 1 cm. We found dysplasia in 12 out of 17 polyps (70.58%) between 1 to 3 cm in size, while we found dysplasia in all 3 polyps (100%) larger than 3 cm.

However, 13 of the smaller polyps with 1 cm diameter are hyperplastic polyps and none of these hyperplastic polyps has dysplasia. Serrated polyps at a size smaller than 1 cm did not have dysplasia. All of the 15 inflammatory polyps were smaller than 1 cm in size, and none was showing the signs of dysplasia. Dysplasia was observed in all polyps examined in the Ki-67 proliferation index. There is a significant relationship between the type of adenoma and the Ki-67 expression, and three of the polyps in the Ki-67 expression were considered dysplasia (Figure 2)

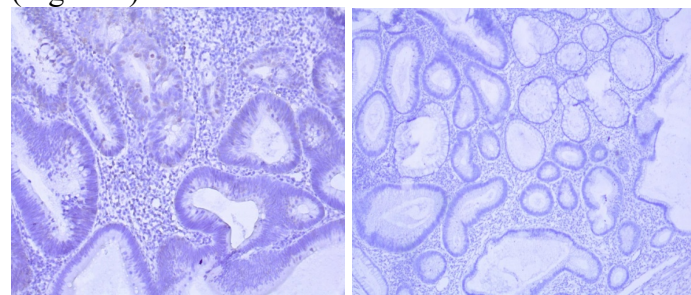


Figure 2. Ki-67 expression in colorectal adenomas.

Discussion

The colorectal carcinomas are the second most common carcinomas in women and the third most common carcinomas in males. So that 90% of colorectal carcinoma cases are adenocarcinoma. (13) The colorectal carcinomas are a multifactorial disease, the majority of which constituting 80 % are sporadic, while the rest of them have an identifiable genetic or ancestral history. It has been shown that the colorectal carcinoma develops from the existing

colorectal polyps, especially a few years after adenomas. The conversion of adenomatous polyps to carcinoma is the widely investigated process and is commonly known as the adenomas-carcinoma sequence. The different features such as size, the number of adenomas, histological type, and grade of dysplasia are the key predictors of the malignant potential determination. (14) The concept of the formation of colorectal cancer from previously existing adenomas has been widely spread based on epidemiological, clinical, postmortem and molecular biological studies. (10) Although this is not a major epidemiological survey, it has generally shown that colorectal cancer was detected in men aged between 50 and 69 (72.34%) constitutes 59.57% of them. Malignancy is detected with the various features such as size, number of adenomas, histological type, and grade of dysplasia, which are the prognosticators of potential malignancy.(14) Tubulovillous changes in polyps have been reported to be associated with malignancy.(15)

In our study, we also observed malignancy over time in tubular adenomas (20%), tubulovillous adenomas (96.57%), and villous adenomas (100%). However, it was worth mentioning that malignancy did not grow in the hyperplastic polyps and the inflammatory polyps. According to the scientific research conducted by Khatibzadeh, Andrei, and Alexander in the Russian Federation, taking into account the pathological parameters, tubulovillous adenomas were dominant in this study and subsequently found to have villous adenomas. (7,8)

As the size of polyps increases, the histopathological changes have also turn out to be heavier. (15) It is known that the large polyps are associated with dysplasia. (23) However, the size is not a certain decisive measure to define it. (15) In our study, we also found 32.5% of the dysplasia in polyps smaller than 1 cm. We observed that 70.58% dysplasia in 1 to 3 cm polyps and 100% of dysplasia in polyps larger than 3 cm. As the size of polyps increases, the histopathological changes have also become heavier. (15) The correlation dysplasia was not observed in the polyps of Ki-67. While evaluating the relationship between the Ki-67 and the immunohistochemical expression of the polyps, it has been shown that there was no significant correlation between age, sex, and type of adenoma. (9)

There was no significant relationship between the Ki-67 expression and the dimensions of the polyps. Thus, 5 polyps having expression are smaller than 1 cm in size, and 3 polyps are 1 to 3 cm. Although there is a general positive correlation between Ki-67 expression of colorectal polyps, it has not been considered statistically significant. The chosen research agrees with the study of Tocantins de Sousa et al,2012 claiming that the expression of Ki-67 was higher in adenomas as well as in adenomas with high-grade dysplasia.(11) The study revealed that the Ki-67 immunohistochemical expression was significantly correlated with the size and degree of dysplasia in colorectal adenomas, but it was found that Ki-67 did not have a significant relationship with the sex, age, and the type colorectal adenomas. Thus, Ki-67 immunohistochemical expression can be considered the part of routine pathological assessments with other conventional prognostic factors in patients with dysplastic colorectal adenomas.

Conflict of Interest

The authors affirm no conflict of interest in this study and the work was not supported or funded by any drug company.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Central Customs Hospital at which the examination process were conducted and with with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The patients who underwent endoscopic polypectomy at the Endoscopy Unit of Central Customs Hospital was examined. Patients with intestinal habitual disorders, bleeding, bloody mucus, constipation for colonoscopy was selected. In addition, patients who have completed the age of 45 and who have applied for screening purposes will be taken to work. Removed polyps were assessed by Tattooing and Hematoxylin Eosin (HE) staining procedure and immunohistochemical expression of Ki-67 at the Department of Pathology of Central Customs Hospital.

Authorship

The two aforementioned authors contributed equally to the study.

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Quantitative evaluation of alkalinizing features of natural mineral waters of Transcarpathia

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Abstract

Introduction. Today latent acidosis resulting from gradual reduction of the buffer reserves of the organism is increasingly the focus of interest because of its role in the development and progression of chronic diseases and comorbidity. One of the promising prophylactic methods of alkalinizing therapy in case of chronic diseases is the correction of the acid-base balance of the body. In preventive medicine, natural mineral waters with predominance of bicarbonate in their anionic composition can be used for alkalinizing therapy. **Aim.** Investigation of the peculiarities of alkalinizing features of natural mineral waters with different total mineralization and composition. **Materials and Methods.** In vitro evaluation of natural alkalinity and alkalinizing profile of mineral waters of Transcarpathia were carried out using in vitro methods and calculation models: assessment of pH, buffering and acid-neutralizing capacity (modified after J.S. Fordtran); calculation of potential renal acid load (PRAL) using physiologically based calculation model (T. Remer & F. Manz). **Results.** Different types of mineral waters were investigated in the study. Due to the geological origin of their formation, almost all types of Transcarpathian mineral waters contain in their anionic composition bicarbonate. It was found that the level of pH for the majority of mineral waters lays in a neutral or slightly alkaline range. Their acid-neutralizing capacity varied from 3 to 244 mmol / 100 ml, the calculated PRAL Index values varied between + 1,57 (for mineral waters with mineralization 0,3 g/l) and - 115,6 (for mineral waters with mineralization 11,6 g/l) indicating their pronounced alkalinizing features. It was also found that PRAL negatively correlated with HCO_3^- , Na^+ , Mg^{++} , Ca^{++} , K^+ content ($p < 0.001$). According to their acid-binding capacity and systemic alkalinizing effect, the studied mineral waters may be classified into two groups. Acid-buffering mineral waters with the index of acid-neutralizing capacity > 40 mmol / 100 ml and negative PRAL Index; the acid-neutralizing pH profile and alkalinizing features of these mineral waters are characteristic for those of antacids. Mineral waters with slightly expressed alkalinity with the index of acid-neutralizing capacity < 40 mmol / 100 ml and negative PRAL Index; their acid-neutralizing influence may be realized due to diluting of gastric juice; they may be used only for the preventive purposes and in cases of slight manifestations of low-grade metabolic acidosis. **Conclusions.** Thus, mineral waters with different content of bicarbonate and mineralization have pronounced alkalinizing features, which may be evaluated quantitatively using complex of in vitro methods and calculation model.

Key words: mineral water, acid-binding and alkalinizing potential, metabolic acidosis,

Introduction

Today latent acidosis resulting from gradual reduction of the buffer reserves is increasingly the focus of interest because of its role in the development and progression of chronic diseases and comorbid conditions associated with chronic diseases of broncho-pulmonar, cardiovascular, digestive, endocrine systems (1, 2).

Over time, ingestion of a high dietary acid load, different medical and toxic influences, overusing of acidosis-formed medications, especially at patients with chronic diseases, can lead to the development and progression of chronic low-grade level of metabolic acidosis. The incidence of this pathological process has been well documented. A chronic acidic load can cause a number of health conditions such as osteoporosis, kidney disease, muscle wasting, rheumatoid disorders, urolithiasis,

bone loss, cardiometabolic diseases, metabolic intoxication with accumulation of such endogenous substances as lactic, pyruvic, conditions. uric acids (1-5). These processes may be a background for the development of polymorbid conditions. Under the of metabolic acidosis, the functioning of hormones, peptides and other regulatory mediators changes, a decrease in the level of insulin and the activity of the hormone. Precise regulations of the acid base homeostasis involves many factors. Even small changes in pH have crucial effects on cellular function. The major buffer system of the organism in the blood is the CO_2 -bicarbonate buffer system. It is the most powerful blood buffer for metabolic acids. The increased acid load can lead to a disruption in acid-alkaline homeostasis in various body compartments and eventually result in chronic

disease through repeated borrowing of the body's alkaline reserves (6-9) and thus, for example, results in calcium-deficit conditions and osteoporosis.

The chronic stage of metabolic acidosis is characterized by extended clinically asymptomatic period and may be revealed only in laboratory studies. Ordinary tests cannot reveal the shift to acidity because humans have an enormous buffer capacity. Mild chronic metabolic acidosis can occur despite normal blood pH and bicarbonate levels. In cases of metabolic acidosis, humans try to eliminate H^+ ions in body fluids. The degree of metabolic acidosis is mild as judged by the degree of the blood acid-base balance, but it cannot be considered mild as judged by its negative physiological effects (4, 5). Also, it must be noted that latent metabolic acidosis is a potentially reversible process under the influence of alkalinizing therapy which promotes upgrading alkaline reserves of the organism and influences the compensation mechanisms. These measures allow stopping the progression of metabolic intoxication and preventing the development of its somatic stage and comorbid conditions. In preventive medicine, natural mineral waters with predominance of bicarbonate in their anionic composition can be used for the purpose of alkalinizing therapy (10-11).

In this context, it was revealed that consumption of mineral waters rich in bicarbonate was suggested to be a suitable source of alkali-formers (12). P. Burckhardt stated that these waters are the most effective practical measures to increase the dietary alkali load (13). A systemic review of the Medline data concerning 150 commercially available European mineral waters was made and their alkalinizing features were calculated using PRAL index (14). The authors of the study examined the question of which nutritional components are conditioning the acidity or alkalinity of mineral waters and their Ca content, in order to define the optimal profile for a positive effect on bone. Other group of investigations testified positive changes in calcium balance and bone metabolism after consuming bicarbonate-rich mineral waters resulting in reduced bone resorption, increased bone formation and improved Ca balance, a decrease in calciuria and of bone resorption markers, increase of calcium level in the hair proving high bioavailability of calcium from the mineral water (15-17). These studies have shown that alkali, bicarbonate-rich mineral waters, especially waters with a strongly negative PRAL value, decrease bone resorption,

even when compared with mineral waters with a higher calcium content, and even in the situation of a sufficient calcium intake, and thus, can contribute to the prevention of bone loss.

A single-centered, randomized trial concerning influence of mineral waters with different bicarbonate content on the diet dependent acid load revealed that consumption of at least 1500-2000 ml of bicarbonate-rich mineral water (> 1800 mg/l) with medium or low PRAL can effectively reduce the net acid excretion reducing the dietary acid load under free-living conditions (2).

Large-scale studies concerning curative efficacy of different types of Transcarpathian mineral waters were performed. Because of predominant presence of bicarbonate in composition, first of all their acid-binding and alkalinizing features were studied (18).

So, natural mineral waters, which contain bicarbonate, represent one of the effective methods of detoxification therapy. Their main effect is alkalinizing and is characteristic in fact for all bicarbonate-rich mineral waters with alkaline or neutral pH. At the same time the level of alkalinizing influence and clinical effect depend on the peculiarities of chemical composition of the given mineral water.

Objective

Investigation of the peculiarities of acid-binding and systemic alkalinizing potential of natural bicarbonate containing mineral waters with different total mineralization and composition.

Materials and methods

In vitro evaluation of natural alkalinity (alkalinizing features) was conducted for different types of Transcarpathian mineral waters in vitro using two groups of indices:

1. the level of the acid-neutralizing features of mineral waters (buffering capacity and acid-neutralizing capacity) after J.S. Fordtran in our modification (19);
2. estimation of systemic alkalinizing features - through the calculation of the PRAL Index (potential renal acid load) using the modified method of T. Remer & F. Manz (20, 21).

Buffering capacity is the indicator for the buffer-antacid features of a given mineral water. It is a chemical indicator, which reflects the ability of mineral water to resist changes in its pH level. It is measured quantitatively by the volume (in ml) of 0,1 N of HCl, which is necessary to change the pH of 100 ml of mineral water per unit.

Acid-neutralizing capacity is a physiological-pharmacological indicator of the expressiveness of acid binding properties of the mineral water. Its value is detected by titration of 100 ml of mineral water with 0.1 N HCl to pH 3.0-3.5. The index reflects the duration of the alkalinizing effect of the mineral water.

PRAL - for bicarbonate containing mineral waters, the PRAL index has a negative value and reflects their systemic alkalinizing effects. The more is its absolute value, the more pronounced are the systemic alkalinizing effects of the given mineral water.

The in vitro measurement of the acid-base ratio of diets is the calculation model developed by Remer & Manz (20). It can also be applied to mineral waters. The PRAL index for each individual mineral water was calculated as described by Wynn et al. (14), using a conversion factor of 0,0146 for SO₄:

PRAL = [0,0146 SO₄ (mg) + 0,027 Cl (mg) + 0,037 P (mg)] - [0,021 K (mg) + 0,026 Mg (mg) + 0,0413 Na (mg) + 0,013 Ca (mg)].

For in vitro evaluation of natural alkalinity (alkalinizing potential) were tested different types of commercially available natural mineral waters of Transcarpathia containing different amounts of bicarbonate.

Results

Due to the geological origin of their formation, almost all types of Transcarpathian mineral waters contain in their anionic composition bicarbonate. The mean values of their acid-neutralizing properties are presented in the Table 1 and Figure 1.

Table 1. Acid-neutralizing properties of natural bicarbonate-containing mineral waters of Transcarpathia

Mineral water	M, g/l	pH	CO ₂ , mg/l	HCO ₃ ⁻ , mg/l	BC, mmol/100 ml	ANC, mmol/100 ml
Pasika	23,8	6,9	1771	14437	206	244
Polyana Kvasova	10,6	6,8	1681	7076	81	105
Polyana Kupil	9,6	6,9	1729	5953	68	92
Luzhanska-7	8,3	6,8	1829	5627	64	92
Nelipinska	3,0	6,4	1199	2226	27	52
Svalyava	5,8	6,4	1496	4132	28	69
Ploskivska	5,0	6,4	1562	3500	38	62
Shajanska-4	4,6	6,1	1900	1830	41	59
Shajanska-242	3,8	6,4	1700	2135	33	51
Sojmi	6,7	6,4	1872	3400	43	62
Drahivska	6,6	6,0	1900	2300	29	42
Kelechinska	1,8	6,0	1800	1450	13	19
Derenivska	0,8	7,2	N	415	3	10
Karpatska	0,6	6,8	90	226	3	4
Uzhgorodska-1	1,8	6,8	1010	350	7	9

Notes: M – total mineralization, BC – buffering capacity, ANC – acid-neutralizing capacity.

The method of titration by 0,1 N HCl is used in US Pharmacopea regulations and regulations of other countries for in vitro evaluation of antacids profile (22). We can see that the highest value of acid binding capacity in the range is 16,55. At the same time, for the bicarbonate-rich mineral waters this value is significantly higher than for commonly used antacids.

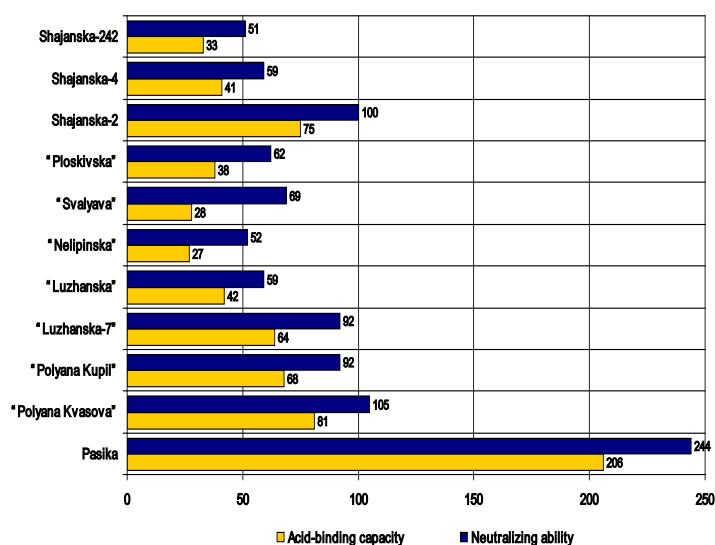


Fig.1. Acid-neutralizing properties of natural bicarbonate-containing mineral waters of Transcarpathia and acid-binding capacity in meq/g for frequently used antacids (US Pharmacopea XXX, method 301)

As it is seen from data presented in the Table 1, the level of pH for the majority of mineral waters varies in a small range (neutral and slightly alkaline), but their buffering and acid-neutralizing capacity varied from 3 to 244 mmol/100 ml.

Depending on the desired effect, the technologies of therapeutic internal use of mineral waters also involve artificial reduction of mineralization (dilution) of high- and medium-mineralized waters using low-mineralized drinking water, as well as their heating to different temperatures. In this case, it is very important to maintain the alkalinizing features of the mineral water at an effective level. It was found, that the dilution of mineral waters leads to approximately proportional decrease of their buffering- and acid-neutralizing capacity levels. At the same time, only a slight decrease in the buffering capacity values was observed, while when heating the mineral water to 37-38°C and 42°C their acid-neutralizing capacity levels in fact remained unchanged (Table 2).

Table 2. Influence of dilution and heating on the acid-neutralizing properties of high-mineralized bicarbonate-rich mineral water in vitro

Mineral water, M 23,8 g/l	Acid-neutralizing properties, mmol/100 ml, temperature, °C		
	20-22	37-38	45-50
	Buffering capacity		
Natural	206,15±5,8	178,8±3,32	176,6±3,14
Dilution 1:1	89,0±3,14	73,0±4,05	72,8±2,24
Dilution 1:2	50,0±3,87	38,6±2,26	27,6±2,26
	Acid-neutralizing capacity		
	20-22	37-38	45-50
	Buffering capacity		
Natural	244,80±1,35	245,3±7,63	240,4±1,35
Dilution 1:1	128,6±2,58	124,0±1,29	127,3±5,16
Dilution 1:2	91,0±1,94	87,6±1,29	80,6±3,23

Notes. M – total mineralization of the mineral water. Changes in the values of acid-neutralizing properties depending on the dilution are statistically valuable ($P < 0,001$), under the influence of heating – statistically unreliable ($P > 0,05$).

To estimate systemic alkalinizing features, PRAL was calculated for some bicarbonate-containing mineral waters. These data are presented in the Table 3. It was found that almost all tested mineral waters had $PRAL < 0$, its value varied between + 1,57 (for mineral water with mineralization 0,3 g/l and - 115,6 (for mineral water with mineralization 11,6 g/l) indicating their pronounced alkalinizing features. It was also found that PRAL negatively correlated with HCO_3^- , Na^+ , Mg^{++} , Ca^{++} , K^+ content ($P < 0.001$).

Table 3. Potential renal acid load (PRAL) Index for Transcarpathian mineral waters

Mineral waters	M, g/l	HCO_3 , mg/l	Mg, mg/l	Na, mg/l	Ca, mg/l	PRAL
Polyana Kvasova	11,6	7625	18,0	3138	96,4	-115,6
Polyana Kupil	9,6	6405	33,8	2547	92,6	-95,4
Shajanska	4,8	3001	29,4	1235	79,3	-43,5
Luzhanska	5,9	4087	29,7	1428	118,6	-53,6
Kelechinska	1,8	1342	33,1	122,1	313,6	-7,1
Ploskivska	6,1	4270	22,5	1386	77,7	-50,5
Sojmi	6,6	3538	67,5	1191	641,3	-30,1
Drahivska	6,6	2806	29,4	1890	108,6	-38,2
Derenivska	0,3	170	11,0	11,0	25,0	+1,57

Note: M – total mineralization of the mineral water.

According to their acid-neutralizing capacity mineral waters containing bicarbonate may be classified into two groups:

- Acid-buffering mineral waters with the acid-neutralizing capacity index value > 40 mmol / 100 ml. Calculated PRAL Index is strongly negative. Their acid-neutralizing pH profile and alkalinizing potential are characteristic for antacids.

- Mineral waters with slightly expressed alkalinity with the acid-neutralizing capacity index value < 40 mmol / 100 ml. Calculated PRAL Index is negative. Their acid-neutralizing influence is maintained due to the dilution effect; they may be used only for the preventive purposes and in cases of slight manifestations of low-grade metabolic acidosis.

The results obtained in vitro were confirmed in clinical studies of alkalinizing effect of a single dose of mineral waters taken into the stomach during intragastric pH-metry. 272 measurements were carried out using bicarbonate containing mineral waters with different mineralization and composition.

When taken into the stomach, mineral waters has two stages of their effect: a short-term deeper alkalinizing of acidic gastric juice to a pH level of 6.5-7.0, which lasts up to 5-10 minutes, then, for another 15-40 minutes (depending on the alkalinizing potential), mineral waters maintain the pH of gastric secret at the level of 3.5-5.0.

Accounting the average duration of alkalinizing effect depending on the level of alkalinizing potential mineral waters were classified into several groups presented in the Table 4. These data allow in vitro conditions to determine the drinking regime for a particular mineral water depending on its alkalinizing properties.

Table 4. Average duration of alkalinizing effect of mineral waters depending on the level of their alkalinizing potential

N	Acid-neutralizing capacity, mmol/100 ml	Duration of alkalinizing effect, min.	
		Corpus	Antrum
1.	< 20	< 10	< 15
2.	20-40	10-12	15-20
3.	40-100	12-17	20-32
4.	100-150	17-20	32-37
5.	150-200	20-25	37-40

Conclusions

We can assume that mineral waters with different content of bicarbonate and mineralization have pronounced alkalinizing potential which may be evaluated quantitatively using different in vitro methods and calculation models. Experimental in vitro and in vivo investigations revealed that mineral water rich in bicarbonate is in fact a functional buffer with certain alkalinizing features which depends on the value of their buffering, acid-neutralizing properties and PRAL Index. These indicators form the objective basis for quantitative evaluation of mineral waters alkalinizing potential and predicting peculiarities of their clinical use.

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I have an arrhythmia. Do I need Cardiac Rehabilitation ?

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Abstract

This review shows that cardiac rehabilitation is not contraindicated in patients with arrhythmias; furthermore, it may be beneficial in reducing the number and severity of arrhythmia episodes. We will briefly describe the most common cardiac arrhythmias for which there is information in the medical literature related to inclusion in a rehabilitation program: inappropriate sinus tachycardia, atrial fibrillation, premature atrial contractions, atrial flutter, premature ventricular beats, ventricular tachycardia. All these data support the use of cardiac rehabilitation for patients with arrhythmia even though this is underused and underappreciated by many clinicians.

Key words: *cardiac rehabilitation, arrhythmia, atrial fibrillation, ventricular premature beats, ventricular tachycardia, atrial premature beats, physical activity,*

Introduction

Cardiac rehabilitation has been shown to be effective in patients with a history of myocardial infarction, percutaneous coronary intervention and aortocoronary bypass (1,2,3). For these reasons, current European and American guidelines recommend cardiac rehabilitation for all these categories of patients (4). On the other hand, being included in a cardiac rehabilitation program not only improves the individual's physical capacity and physical quality, but has also been shown to decrease mortality by decreasing the number and severity of arrhythmic events (5).

Cardiac arrhythmias, depending on their type, from the simplest to the most severe, can have consequences on the patient's life: from panic attack to heart failure, stroke and even arrhythmic death. In addition to antiarrhythmic treatment and catheter ablation, the cardiologist should consider lifestyle changes. Because physical inactivity is an essential risk factor for cardiovascular disease, it should be borne in mind that, with the recommendations of antiarrhythmics, cardiac rehabilitation should also be recommended, with a progressive increase in

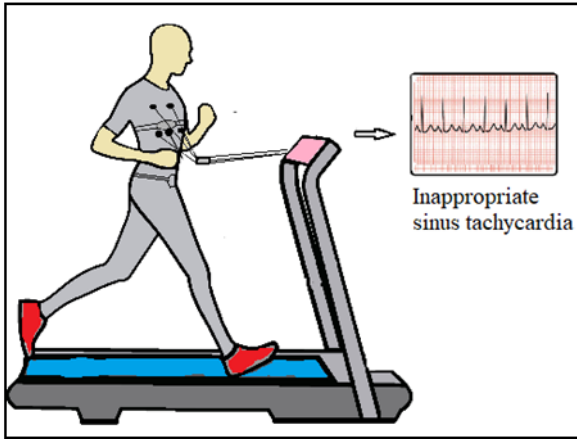
physical activity. Both adults and old patients (6) benefit from rehabilitation (7,8,9).

Rehabilitation can also be performed in patients with implanted devices: pacemakers, ICDs, CRTs (10,11). In Romania there are hospitals and centers that can perform cardiac rehabilitation, and arrhythmias should be one of the indications for starting rehabilitation.

This review will show that cardiac rehabilitation is not contraindicated in patients with arrhythmias; furthermore, it may be beneficial in reducing the number and severity of arrhythmia episodes. We will briefly describe the most common cardiac arrhythmias for which there is information in the medical literature related to inclusion in a rehabilitation program.

Certainly, cardiac rehabilitation will be delayed in patients with severe sustained ventricular tachycardia or ventricular fibrillation, unstable angina or acute myocardial infarction, severe hypertension, intracardiac ventricular thrombosis or pedicles until the status of the patient permits physical activity.

1. 1. Inappropriate sinus tachycardia.



It is a form of arrhythmia characterized by an excessive increase in the sinus rate in response to low intensity effort. It is defined as a resting heart rate of over 100 bpm or an average heart rate > 90 bpm during 24-hour Holter ECG in the absence of reversible causes such as hyperthyroidism, anemia, fever, hypovolemia, hypoxia, central nervous system stimulation, diabetic dysautonomia, etc. In inappropriate sinus tachycardia the P wave has a sinus morphology in the 12-lead electrocardiogram. One of the mechanisms that explain arrhythmia is the increase of sinus node automaticity. The treatment methods of inappropriate sinus tachycardia include: antiarrhythmic drugs, catheter ablation and cardiac rehabilitation.

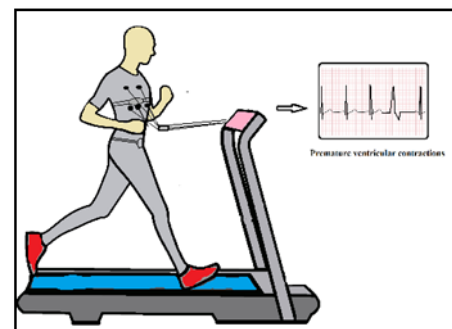
The rehabilitation of patients with inappropriate sinus tachycardia implies the following general measures: 1) sleeping with the head raised to 30 degrees, 2) proper hydration, 2-2.5 liters/day, 3) endurance training, 5) back pressure maneuvers and 6) proper salt consumption, above 10-20 mg/day. 7) Elastic compression stockings are useful in patients with venous insufficiency of the lower limbs (12).

Before starting the cardiac rehabilitation program, tests are carried out to evaluate the sympathetic/parasympathetic autonomic system: 1) the cold water test (also used in patients with paroxysmal supraventricular tachycardia as a method of treatment) induces bradycardia by activating the parasympathetic system during application of cold water on the face, which sends efferent signals to the cardiac parasympathetic ganglia. In patients with inappropriate sinus tachycardia, the response is abnormal with the appearance of tachycardia instead of bradycardia; 2) the isoprenaline test - which shows an excessive increase in heart rate after its administration; 3) evaluation of the intrinsic heart rate after

administration of propranolol and atropine (which blocks sympathetic and parasympathetic efferent signals to the heart), which confirms the increase of sinus node automaticity; and 4) the response to the Valsalva maneuver, which shows an abnormal relationship between the maximum heart rate and the minimum heart rate recorded during the maneuver. After completing the cardiac rehabilitation program, all these values are checked again and compared with those recorded at the beginning of the training program (13).

The Levine program was proposed for patients with inappropriate sinus tachycardia and orthostatic postural tachycardia. It includes 3 months of physical training associated with lifestyle changes: sleeping at 30 degrees head tilt, water intake 3 liters/day and salt intake 10 grams/day. Both before and after cardiac rehabilitation, the patients are tested for sympathetic/parasympathetic imbalance (13).

2. Cardiac Rehabilitation in patients with Premature Ventricular Contractions

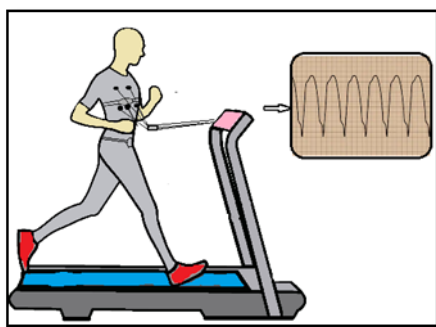


Premature ventricular contractions are present in more than 6% of middle-age adults. Their incidence increase with age, low potassium or magnesium levels, history of structural heart disease, and hypertension. There are studies on patients with PVCs that performed cardiac rehabilitation. Lillis et al verified the effect of physical training during cardiac rehabilitation on the the number of ventricular premature contractions in 18 patients performing included in a cardiac rehabilitation program. Patients with stable ischemic heart disease were divided into two groups: 9 with a high risk of cardiovascular events and 9 with low risk. All 18 patients were followed by Holter EKG during physical exertion as well as during resting period. Physical exercise was performed on ergometric bicycle or treadmill, 40 minutes daily at an intensity of 75% of maximum METS or 85% of the maximum theoretical heart rate.

Results showed that during the days with physical training, the number of ventricular premature contractions in Holter EKG was higher than during resting days. Compared to the low risk group, in the high risk group the number of premature ventricular contractions was higher during effort or immediately after stopping the effort. During sleep or during sexual activity, the number of ventricular premature contractions did not increase. Patients in both groups were followed for 7.5 years and no deaths were recorded in any of the groups (14).

The study of Boukhris et al. on 122 patients with 59 diabetic and 63 non-diabetic patients, demonstrated 2 essential things: 1) cardiac rehabilitation in diabetic patients improves repolarization parameters (corrected QT interval and QT interval dispersion) and 2) the number of ventricular premature contractions evaluated by Holter EKG in both diabetic and non-diabetic patients decreased at the end of the rehabilitation program. In addition, the severity of ventricular premature contractions expressed by the Lown class decreased at the end of the rehabilitation program in both diabetic and non-diabetic cat patients (15).

3. Cardiac rehabilitation in patients with Ventricular Tachycardia and Ventricular Fibrillation

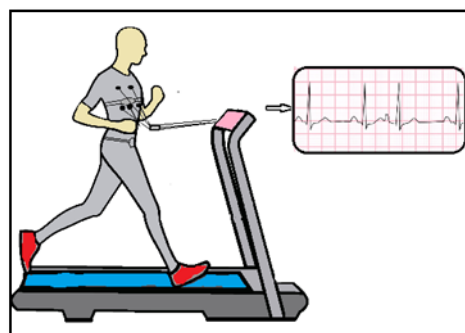


Patients with ventricular tachycardia and fibrillation may undergo cardiac rehabilitation, obviously outside the acute episode, when the patient is free of ventricular arrhythmias. Even after repeated episodes of ventricular tachycardia or ventricular fibrillation, cardiac rehabilitation can be performed. This is the case of patients with electrical storm. Electrical storm is defined as frequent episodes of ventricular tachycardia or ventricular fibrillation occurring within a short period of time. Obviously it is a life-threatening arrhythmia and the treatment consists of antiarrhythmic drugs or catheter ablation.

It is very important after an episode of electrical storm to prevent the occurrence of recurrences and an important place is occupied by cardiac rehabilitation. It increases the physical capacity, allows daily activity, and for hospitalized patients, allows safely discharge (4).

The study of Kato et al. evaluated the feasibility of cardiac rehabilitation in patients with electrical storm. The study included 67 patients divided into 2 groups: the cardiac rehabilitation group (which included 39 patients) and the non-rehabilitation group (which included 28 patients). The results showed: regarding the recurrences of electrical storm between the 2 groups, the percentages were not statistically different (13% vs. 21%). Furthermore, the number VT and VF episodes were similar between the 2 groups (28% vs. 25%). However, mobilization within the first 48 hours after the electric storm had adverse cardiac effects: recurrent electric storm (21% vs. 6%) and recurrent VT / VF (34% vs. 19%) in the early mobilization group compared to the late mobilization group. Furthermore, early mobilization within the first 48 hours was associated with higher BNP values, and lower ejection fraction. On the other hand, in the group without cardiac rehabilitation there were 3 deaths by uncontrolled ventricular arrhythmias, in contrast to no deaths in the group undergoing cardiac rehabilitation. Another important result was that daily physical activity significantly improved in the cardiac rehabilitation group (16).

4. Cardiac rehabilitation in patients with atrial premature contractions.

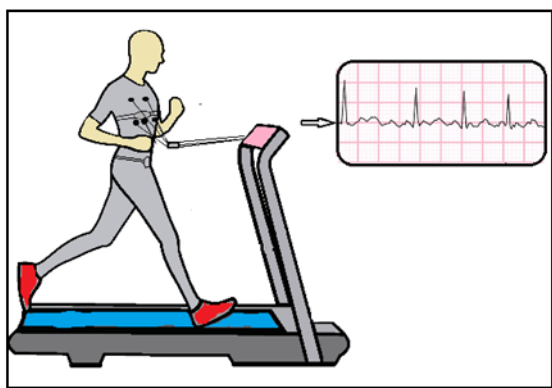


Premature atrial contractions are common arrhythmias and are found both in patients who want to start a cardiac rehabilitation program and in patients who perform exercise training. Physical exercise leads to an increased plasma concentration of circulating catecholamines, which may be an inducing factor for the occurrence of premature

atrial contractions. For these reasons, the first line of treatment in this case is the administration of beta blockers. It is also well known that cardiac rehabilitation decreases the plasma concentration of adrenaline and noradrenaline. For these reasons, rehabilitation can be performed and is totally indicated in patients with premature atrial contractions.

Younis et al. included 213 patients with premature atrial contractions in a 6-month cardiac rehabilitation program, consisting of 2 sessions/week of exercise, lasting 60 minutes. Premature atrial contractions were present before inclusion in the rehabilitation program, being revealed during an initial stress test. At long-term follow-up it was confirmed that patients with premature atrial contractions had a 2-fold increased risk of atrial fibrillation. On the other hand, the incidence of major cardiac adverse effects and mortality was similar in the group with premature atrial contractions and in the group without premature atrial contractions (17).

5. Cardiac rehabilitation in patients with Atrial fibrillation



Atrial fibrillation is the most frequent cardiac arrhythmia. Therefore, patients who already had an episode of AF should be advised regarding their physical, psychological and social life. Thus, the cardiologist makes recommendations on the physical exercise and lifestyle modifications in order to stabilize, slow down or even reverse the underlying arrhythmic process. Patients with both paroxysmal and persistent/permanent atrial fibrillation can be re-included in socio-professional and family life (18).

Since the 1990s, the problem of an increased risk of atrial fibrillation has been raised in individuals practicing high intensity endurance sports. Endurance sports can precipitate dilation of the left atrium, hypertrophy of the left ventricle and alterations of the autonomic cardiac nervous system. On the other hand, moderate intensity sport has been shown to lower blood pressure levels, decrease left ventricular hypertrophy, and reduce dilation of the left atrium. Furthermore, the Legacy study showed that moderate intensity sports lead to weight loss, and indirectly reduce the number of episodes of atrial fibrillation and also the length of AF episodes. The results are similar to those of Mozaffarian et al., which confirm that moderate physical activity in patients aged over 65 years reduces the risk of atrial fibrillation by 28% compared to patients who do not practice sports. At the same time, a study published by Azarbal et al. on an impressive number of > 90,000 women with a mean age of 63 years showed that physical exertion of 15 MET x hour leads to a significant decrease in AF episodes compared to women who practiced <1 MET x hour (19).

Depending on the type of atrial fibrillation, the way cardiac rehabilitation is performed differs from case to case. In patients with the paroxysmal (or non-permanent) form, the role of rehabilitation is to prevent other episodes of AF, whereas in patients with the permanent form, the objective is to control heart rate. The same goal is that of drug treatment in patients with paroxysmal and permanent AF, so cardiac rehabilitation is actually a substitute for medication.

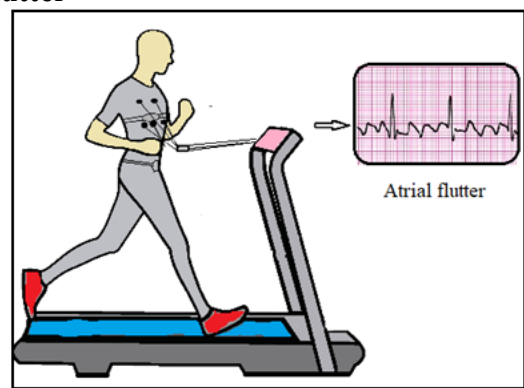
In the study of Mozaffarian, 51 patients with non-permanent AF were included and divided into 2 groups: the cardiac rehabilitation group and the control group. Interestingly, patients in both groups were monitored by a loop recorder, all of them agreeing with the subcutaneous implantation of the monitoring device. The monitored period was 4 weeks before rehabilitation and 4 weeks after completion of the cardiac rehabilitation program. As a result, in the rehabilitation group the duration of AF episodes decreased from 8.1% to 4.6%, while in the control group it increased from 10.4% to 14.6%, the difference being statistically significant. In addition to these results, an important benefit was observed on the left ventricular systolic function evaluated by echocardiography, quality of life and lipid profile after completion of the rehabilitation program (19).

In the CARDIO-FIT study, conducted in Adelaide, Australia, patients with non-permanent atrial fibrillation were included, all of them obese with a BMI > 27 kg/sqm. Initially, low intensity physical activity was recommended for 20 minutes, 3 times per week, which was gradually increased to 200 minutes of moderate intensity/week. The maximum heart rate allowed during exercise was 85% of the theoretical maximum heart rate (220-age), and the patients were advised to avoid reaching this rate. A treadmill stress test was performed, using Bruce's protocol, before the inclusion in the program and at the end of the rehabilitation program. In patients whose cardiac rehabilitation had a beneficial effect defined as > 2 MET improvement, there was a significant decrease in weight, a significant decrease in blood pressure and the number of hypotensive drugs used, a significant decrease in cholesterol, triglycerides and hypolipidemic drugs, glycosylated hemoglobin, blood glucose, a decrease in high-sensitive C-reactive protein (hs-CRP), a decrease in the number and duration of AF episodes and a decrease in the number of AF recurrences after conversion to sinus rhythm or catheter ablation. The authors conclude that each MET of physical capacity improvement leads to a 20% decrease in AF recurrences in obese patients (20).

In patients with permanent atrial fibrillation, circumstances are different because it is no longer possible to prevent recurrences or decrease the duration of AF episodes. The goal is to decrease the heart rate during rest and effort and to reduce the need of antiarrhythmic drugs. Osbak et al. published in 2011 a study on 49 patients with permanent AF which were included in a cardiac rehabilitation program. The program consisted of 12 weeks of intermittent training composed of 3 sessions x 1 hour per week training. Each session contained: heating, high intensity training and deceleration or gradual return to rest. The results showed a higher intensity reached during the stress test in the rehabilitation group compared to the control group, and a longer distance for the 6 minute walk test, with a decrease of the resting heart rate. At the same time, the quality of life improved in the cardiac rehabilitation group, demonstrating the beneficial effects of cardiac rehabilitation in patients with permanent atrial fibrillation (21).

Another randomized study of 30 patients with permanent AF showed an improvement of the exercise capacity and heart rate variability after 2 months of training. Pliene et al. studied the change of heart rate in 10 patients with permanent AF who underwent cardiac rehabilitation with moderate physical training (45 minutes of walking or jogging 2 times a day). They demonstrated that physical training controls heart rate in patients with permanent AF similarly to beta blockers and digoxin, inducing a decrease in the mean heart rate on Holter ECG from 76/min to 67/min (approximately 12%) (22).

6. Cardiac rehabilitation in patients with Atrial Flutter



There are few studies examining the effect of exercise training in patients with atrial flutter. Most of the studies are performed in patients with atrial fibrillation but also include patients with atrial flutter in the analysis, because of the similarity between the 2 arrhythmias.

A Norwegian study followed up endurance athletes over a 10-year period and described the number of individuals who developed atrial flutter during this period (23). Out of 3545 men, 52 had atrial flutter. On the other hand, there was a dose-response relationship between the total duration of endurance sports and the risk of developing atrial flutter in men over 53 years. Thus, the authors declare that this is the first study to establish a dose-response link between endurance training and atrial flutter. One of the strengths of this study was that investigators were able to differentiate between atrial fibrillation and atrial flutter based on ECG recording. Even if the patients had similar symptoms, differentiation is still possible due to the morphology of the atrial P wave on the 12 lead ECG.

Conclusion:

Cardiac rehabilitation is a valuable treatment for a large spectrum of patients with cardiac arrhythmias. Its benefits are based on research that demonstrates a decrease in the number and duration of arrhythmia episodes, an improvement in quality of life, psychological status, and a decrease in morbidity and mortality. It also reduces the hospitalization duration and readmission. All these data support the use of cardiac rehabilitation for patients with arrhythmia even though this is underused and underappreciated by many clinicians.

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THE EFFECTS OF PHYSIOTHERAPY PROGRAMS IN THE RECOVERY OF CALCANEAL SPURS

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Abstract

The calcaneal spurs are a specific condition of middle and old age. It manifests through plantar osteophytosis on plantar fascia insertion, and is largely associated with plantar fasciitis. Calcaneal spurs are asymptomatic until they are mechanically irritated and inflamed, they respond through a local intense pain. The proposed treatment is conservative, and uses physiotherapy applied locally such as TENS current, ultrasound and passiv/active stretches. The study was performed on a group of 10 patients, treated daily with the physiotherapy complex program. Patients are evaluated according to the VAS pain assessment scale at the beginning of the treatment and at the end. The evaluated parameters were: pain at rest, pain in standing position, and pain in walking. The results showed a favorable evolution in pain reduction, in all patients treated within 10 days. All the data obtained from the evaluations were processed statistically based on specialized software.

Key words: *heel pain, calcaneal spur, physiotherapy, plantar fasciitis,*

Introduction

Heel pain is a very common reason why patients go to the orthopedics, rheumatology and physiotherapy medical offices. The calcaneal spur is a bony protrusion that appears at the level of the Achille's tendon insertion and / or at the level of the planar fascia (1). The differential diagnosis is essential in the optimal treatment of calcaneal osteophytosis; it is making the difference between plantar fasciitis, ahilian tendinopathy, Haglund's disease, calcaneus fractures and, rarely, calcaneous bone tumors (2).

Heel spurts most commonly occur at the plantar fascia insertion on the heel. Spurs may also appear anywhere along the calcaneal tuberosity. The calcaneal spurs are usually asymptomatic, and their inflammation is manifested by intense local pain. The pain is caused by the irritation and inflammation of the fibers from the insertion of the plantar fascia at the level of the medial tuberosity of the heel. It can be said that painful calcaneal spurs are associated with plantar fasciitis and more rarely with inflammatory systemic diseases such as: Gout, rheumatoid arthritis, Reiter syndrome, etc.. Some patients develop heel spurs due to high impact exercises on the heels, and in others, has a strictly mechanical cause, determined by the abnormal gait and the way in which the heel attack is performed in the gait cycle (3).

The causes of the emergence of plantar calcaneal spur are multiple and here we mention abnormal mechanical forces of the muscles: soleus, extensor hallucis brevis, flexor digitorum brevis, extensor digitorum brevis, quadratus plantae gastrocnemius, plantaris, abductor digiti minimi and abductor hallucis (4). Another cause is the accumulation of repetitive traumas at the level of the heel, traumas that will generate tears and cracks in the plantar fascia in the attachment area.

Individual occupation, obesity, age, diabetes, osteoarthritis and biomechanical disorders of the foot are other predisposing factors for the appearance of the spleen. Chronic local inflammation is the result of attempts to repair the lesions of the fascia, entering a negative loop in which the production and maintenance of symptoms is a consequence of the constant irritation and tension of the fascia [5].

It is considered calcaneal spurs from 2 mm upwards, and all changes under this dimension are considered irregularities of the cortical bone. The vast majority of the calcaneal spurs are asymptomatic, accidentally finding themselves on the profile incidents of the calcaneal radiographs. Several meta-analyzes have demonstrated the relationship between heel pain and calcaneal spurs. The pain is directly proportional to the size of the spur, with the level of compression of the inferior calcaneal nerve, with the inflammation of the spur, with the thinning and deformation of the fat layer surrounding the heel, and the plantar fasciitis [6].

Material and method

The study profile was created and conducted on a pilot group of ten patients diagnosed and treated in the Micromedica Medical Clinic from Piatra Neamt, six female and four male. All patients were diagnosed by the orthopedic specialist doctor, they were between 39-67 years old. Two age groups were identified 39-50 years and 50-67 years old. All diagnosed patients, were evaluated and confirmed radiologically by specialist doctor, by performing a standard X-Ray foot profile image. Radiologically, the calcaneal spur presents itself as a bony exostosis on the sagittal image projecting inferomedially from the calcaneus (7).

The patients were evaluated before and after treatment from the perspective of the pain severity, using the VAS scale (0 painless and 10 with unbearable pain) and goniometry to test ankle Range of Motion (RoM) (8). The VAS scale was used to assess pain in rest, pain in station and pain in walking. The dimensions of the plantar spurs were noted, ranging from 5 to 20 mm. Ankle RoM dorsal flexion (20-30 degrees normal) and planar flexion (40-50 degrees normal) were measured on before and after the physiotherapeutic treatment.

Calcaneal spur more than 10 mm is associated with plantar fasciitis, determined by clinical examination in six out of ten patients.

Inclusion criteria for subject selection:

- Subject *approval* by signing *informal consent form*;
- Subject age: more than 18 years;
- Gender: male or female;
- The failure to include the subject in one of the exclusion criteria in the clinical investigation;
- The subject was diagnosed by calcaneal spurs over 5 mm by the specialist medical doctor;
- The subject was diagnosed with calcaneus spurs, sent on the basis of a medical letter to the physiotherapy department, by the specialist medical doctor.

Exclusion criteria for subject selection:

- The subject's refusal to sign the *informal consent form*;
- Subject that is part of the vulnerable populations;
- Subject age: less than 18 years.

All patients underwent a physiotherapy program for 10 consecutive days, in which electrical procedures TENS, ultrasound and passive and active stretches were applied on the sole. TENS currents were applied 30 minutes on a single channel in 6 patients and with two channels in 4 patients. Ultrasound therapy was performed in pulsed trains with 10% duty-cycle, with a probe power of 0.3 to 0.4 W / cm², for 4 to 6 minutes. The passive stretches were performed by the physiotherapist as well as at his request, the patient to perform the active stretching (9-10).

In order to statistically process and compare the data obtained from the patient evaluation, a specialized software was used IBM XI Statistics. The input and output data were recorded, inventoried, processed and relevant information was obtained on the evolution of patients in a cycle of 10 sessions of physiotherapy.

Results

All the data was generated by the clinical evaluation and patient history, and they served as the primary source of information, binding the clinical aspects of the size and disposition of the calcaneal spurs, to gender of the patients, and the conditions that are closely related to the appearance of the spurs. Two age groups were identified: 39-50 years, and 50-67 years old.

In the table no. 1 we have described the particularities of the 10 patients with calcaneal spurs, of which 4 with bilateral placement and with important dimensions - 14 up to 20 mm. The plantar fasciitis was present in 6 of 10 cases, and 3 patients also presented Haglund's disease, with spurs ranging from 10 to 20 mm.

Table no. 1. patients with calcaneal spur (disposition by sexes, size of spurs, interested area, associated diseases)

	age	sex	Spur size	Arrangement	Plantar fasciitis	observations
P1	39	female	10 mm	plantar	yes	
P2	41	female	14 mm	plantar	yes	
P3	64	female	20 mm	plantar and posterior	yes	Haglund
P4	45	female	8 mm	plantar	no	
P5	55	female	5 mm	plantar	no	
P6	43	female	9 mm	plantar	no	
P7	65	male	15 mm	plantar	yes	
P8	67	male	18 mm	plantar and posterior	yes	Haglund
P9	57	male	9 mm	plantar	no	
P10	59	male	16 mm	plantar and posterior	yes	Haglund

Legend: P.1 – patient 1, P.2 – patient 2, P.3 –patient 3, P.4 – patient 4, P.5 –patient 5, P.6 – patient 6, P.7 – patient 7, P.8 – patient 8, P.9 –patient 9, P.10 –patient 10

Table no. 2. Initial VAS pain assessment

	VAS rest	VAS in stationary	VAS in walking
P1	3	4	5
P2	3	6	7
P3	4	6	6
P4	2	4	4
P5	2	3	3
P6	4	4	5
P7	4	6	7
P8	3	4	6
P9	3	3	4
P10	4	6	6

Legend: P.1 – patient 1, P.2 – patient 2, P.3 –patient 3, P.4 – patient 4, P.5 –patient 5, P.6 – patient 6, P.7 – patient 7, P.8 – patient 8, P.9 –patient 9, P.10 –patient 10

Table no. 3. final VAS pain assessment

	VAS rest	VAS in stationary	VAS in walking
P1	1	2	3
P2	2	3	3
P3	2	3	3
P4	1	2	2
P5	1	2	2
P6	2	2	4
P7	2	2	3
P8	2	3	2
P9	1	1	2
P10	2	3	3

Legend: P.1 – patient 1, P.2 – patient 2, P.3 –patient 3, P.4 – patient 4, P.5 –patient 5, P.6 – patient 6, P.7 – patient 7, P.8 – patient 8, P.9 –patient 9, P.10 –patient 10

Three parameters of pain were followed using the VAS scale. In table no.2 the input data represent the start of the treatment evaluated in three diferent positions: pain in resting, pain in stationary position, and finally the pain during the normal gait. Following the execution of the 10 physiotherapy sessions, the same three output parameters were evaluated - the pain decreasing progressively in rest, in stationary and in walking (table no. 3).

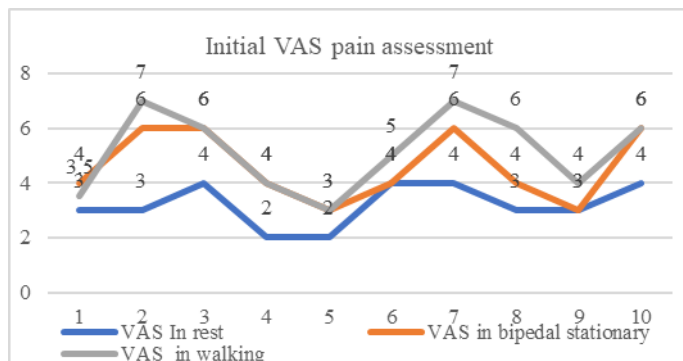


Figure no 1. Initial VAS pain assessment

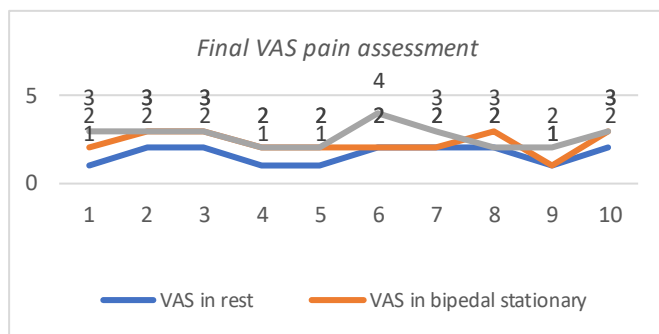


Figure no 2. Final VAS pain assessment

Table no. 3. VAS pain assessment correlations in three diferent positions between initial and final tests

VAS R-I	VAS BS-I	VAS W-I	VAS R-F	VAS BS-F	VAS W-F
3	1	4	2	5	3
3	2	6	3	7	3
4	2	6	3	6	3
2	1	4	2	4	2
2	1	3	2	3	2
4	2	4	2	5	4
4	2	6	2	7	3
3	2	4	3	6	2
3	1	3	1	4	2
4	2	6	3	6	3
0.763762616	0.676752968	0.480020451			

As can be seen from table no. 3 and table no. 4, there are values of the two variables from the initial and final tests of the three positions evaluated, values that represent strong but even weaker negative correlations.

It can be found in Figure 3 (correlations of all the three positions assessed) that strong negative correlations predominate, which leads us to conclude that the recovery programme of the 10 physiotherapy sessions has achieved its purpose, pain felt in the three evaluated positions.

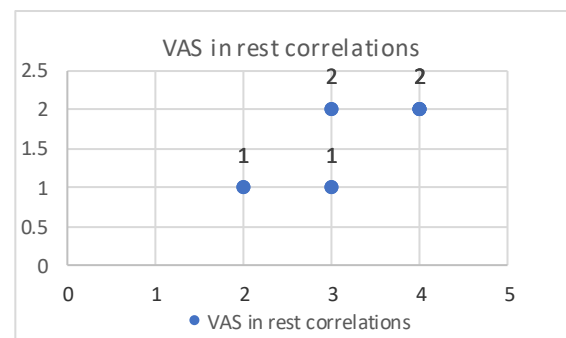


Figure no 3. VAS in rest correlations

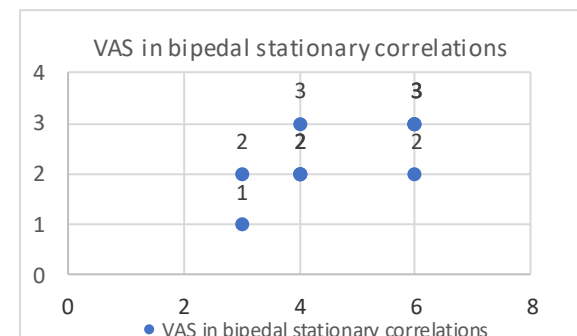


Figure no 4. VAS in bipedal stationary correlations

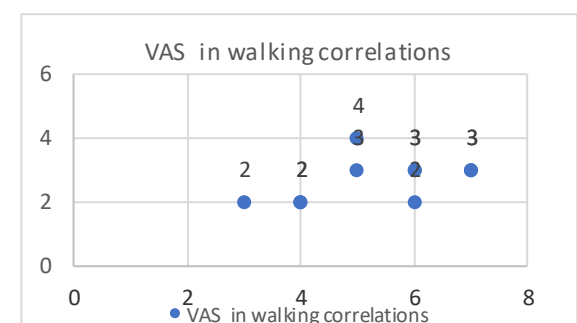


Figure no 5. VAS in walking correlations

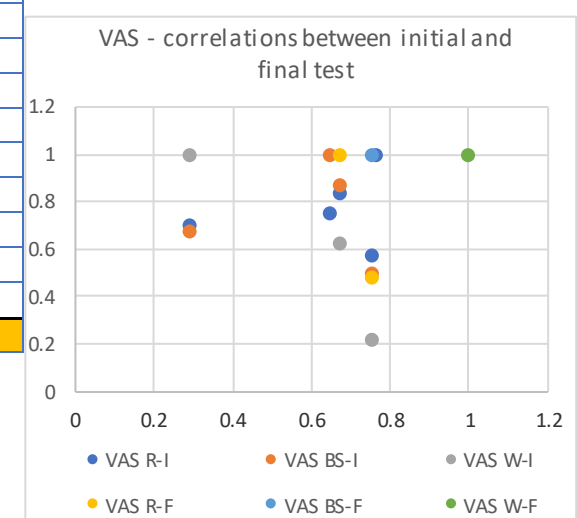


Figure no 6. VAS - correlations between initial and final test

Table no 4. VAS - Correlations between initial and final test

VAS	VAS R-I	VAS BS-I	VAS W-I	VAS R-F	VAS BS-F	VAS W-F
VAS R-I	1					
VAS BS-I	0.763762	1				
VAS W-I	0.645881	0.7484552	1			
VAS R-F	0.292174	0.7013343	0.6767529	1		
VAS BS-F	0.674020	0.8365362	0.8669214	0.627719	1	
VAS W-F	0.751305	0.5738190	0.4945502	0.219512	0.4800204	1

In table No. 4 we note that the values of the Pearson correlation coefficient has trends toward absolute value ($-1 < r_{xy} < +1$) which results as the intensity of the linear relationship between the two variables (pair to pair) is higher. Also, figure No. 6 can again be distinguished that the relationship between the two variables is almost compact and tends in a clear direction.

Table no 5. Dorsal and Plantar Flexion - Initial and Final Test Correlations

	Dorsal Flexion I	Dorsal Flexion F	Plantar Flexion I	Plantar Flexion F
P1	25	25	40	40
P2	20	20	42	42
P3	9	15	24	31
P4	20	20	37	39
P5	18	20	36	41
P6	22	22	41	42
P7	10	16	29	33
P8	11	14	27	36
P9	17	18	38	38
P10	11	16	29	35
CORREL	0.960690616		0.923747489	

Regarding the correlation between the initial and final tests of dorsal and plantar flexion we can say that the two values obtained represent each a very good correlation following the α significance test.

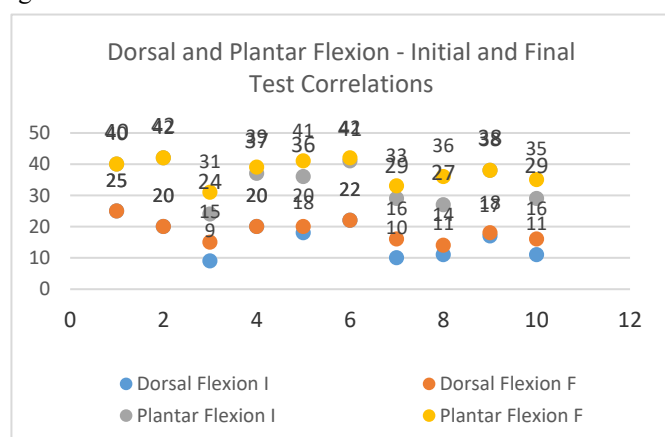


Figure no 7. Dorsal and Plantar Flexion - Initial and Final Test Correlations

At the same time, from table no. 7 we can conclude that those values, of the correlation coefficient in the case of dorsal flexion of 0.960690616, respectively the plantar flexion of 0.923747489 are high values (according to the Rules of Colton) which means a degree of very good association, so a strong correlation.

In this situation we can say that the recovery programme established during the 10 physiotherapy sessions described resulted in a slow but effective regression of the final values on the VAS scale, but also an increase in joint mobility in dorsal and plantar flexion.

Conclusions

In this situation we can say that the recovery programme established during the 10 physiotherapy sessions described resulted in a slow but effective regression of the final values on the VAS scale, but also an increase in joint mobility in dorsal and plantar flexion. All authors contributed equally to this manuscript.

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Tear biomarkers in neurodegenerative diseases

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Abstract

In neurodegenerative diseases (NDD) early and accurate diagnosis is a priority in neurological research, as treatment is most effective when started early in the disease evolution. Biomarkers could be used as an assessment tool for high risk population, for monitoring disease progression and evaluation of treatment efficacy. The close connection between the eye and the brain leads to the hypothesis of detecting biomarkers for neurological diseases in tear fluid, collected by non-invasive methods and with a relatively stable composition.

A combination of four tear proteins (lipocalin-1, lysozyme-C, lacritin and dermcidin) is demonstrated to be specific for Alzheimer’s disease (AD). Asymptomatic patients which showed increased volume and protein content of tear secretion, and decreased levels of lipocalin-1, lysozyme-C and lacritin and increased levels of dermcidin, may be considered at risk of developing AD, and may be subjects to further psychological and neuroimaging tests.

In Parkinson’s disease (PD), tear levels of oligomeric α -synuclein are considered to be a strong biomarker. Also, high tear levels of oligomeric α -synuclein could precede the onset of clinical manifestations of PD, with possible utility as screening tool in asymptomatic people. The diagnosis of NDD through the eye window could be an important step forward in personalized medicine.

Key words: *neurodegenerative diseases, fluid biomarkers, tear composition,*

Introduction

Neurodegenerative diseases (NDD) are a group of age-dependent, chronic disorders characterized by progressive dysfunction and loss of neurons, which became increasingly prevalent. Pathogenesis is related to deposition of proteins with altered physicochemical properties in brain cells (misfolded proteins), followed by the involvement of different functional systems in the nervous system, with specific clinical presentation (1).

Early and accurate diagnosis of NDD before the occurrence of clinical symptoms is a priority in neurological research, as treatment is most effective when started early in the disease evolution. Usually, the methods currently available have less applicability for the screening of general population, and there is a high demand for novel diagnostic methods using non-invasive and accessible tools for detecting NDD in their pre-clinical stage or groups of high-risk individuals.

Biomarkers are a useful tool in detecting the risk of developing a disease, in assessing the rate of disease

progression and activity, and in predicting the response to a specific therapy (2). A biomarker is a “defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions” (3).

Biomarker levels in biofluids (serum, plasma, cerebrospinal fluid or tears) have been measured in several NDD, with the aim of finding a diagnostic or prognostic parameter (4). Biomarkers collected by noninvasive methods are valuable, especially for screening high-risk populations.

Tears are an accessible body fluid, with relatively simple composition and non-invasive sample collection. There are four types of tears: basal, reflex, emotional and closed eye. Samples are collected through Schirmer strips, minisponges, microcapillary tubes or eye-wash, without inducing reflex tearing, and should be stored in standard conditions (5,6).

The lacrimal glands are part of the “lacrimal functional unit”, together with the ocular surface (cornea, conjunctiva and meibomian glands) and the interconnected sensory and motor nerve fibers (7). The volume and the composition of the tear film is controlled by this unit, and consequently, the secretion of specific tear proteins is influenced by changes in neuronal function. The lacrimal glands are innervated by autonomic sympathetic and parasympathetic nerves; the cholinergic nerves stimulates the tear secretion. The flow rate of tears is thus influenced by autonomic pathways, and is highly sensitive to autonomic dysfunction (8,9,10). Tear functions consist in lubrication of the eyelids during blinking, maintaining homeostasis of eye surface and preservation of the corneal surface (11). The tear film creates a chemical and immunological barrier at eye's surface, protecting against physical and biological agents (12).

Tear biomarkers in clinical practice

Tear film is formed by a muco-aqueous layer, which contains proteins, and a lipidic layer (11). Tears contain a mixture of proteins, peptides (including between 1500 and 2000 types identified by proteomics), lipids (6 classes with 150 species), mucins, small molecule metabolites (100 types identified), nucleic acids (microRNAs), electrolytes and water, secreted from lacrimal glands, Meibomian glands, goblet cells and ocular surface epithelial and nerve cells (2,10,13,14,15). The assessment of tear composition represents an ideal tool for biomarker detection.

Tear protein content is high, between 6-10 mg/ml, and the major tear proteins, such as lipocalin-1, lactotransferrin and lysozyme-C, are involved in local immunologic and inflammatory processes (9,16). Two thirds of the proteins are tear-specific, and one third is common with plasma proteins (10). Multiple tear biomarkers have been described in ocular diseases such as: dry eye disease (DED), diabetic retinopathy, glaucoma, giant papillary conjunctivitis, vernal kerato-conjunctivitis, peripheral ulcerative keratitis, Sjorgren's syndrome (SS), thyroid-associated orbitopathy (TAO), etc. In this group, useful biomarkers detected were: lactoferrin, matrix-metalloproteinase-9 (MMP-9) - for DED, inflammatory cytokines (interleukin-8, interferon-gamma, tumor necrosis factor-alpha, interleukin-1, interleukin-6, -17, -22, etc) and chemokines – for DED, TAO and SS (2,17).

Tear composition is a source of biomarkers in systemic diseases, such as: diabetes, systemic sclerosis, cystic fibrosis, rheumatoid arthritis and cancer (2,10). Lacryglobin was shown to be secreted in higher amounts in the tears of patients with colon, prostate, breast and lung cancers (18).

Tear biomarkers in neurodegenerative diseases

The close connection between the eye and the brain leads to the hypothesis of detecting specific ocular biomarkers for neurological diseases (2). Biomarkers in NDD could be used as risk assessment in general population, monitoring of disease progression and evaluation of treatment efficacy. The eye shares neural similarities with the brain, and is considered to be a target in the research field of biomarkers in NDD (19).

For the anterior pole, tear fluid is one of the most important source of biomarkers, as changes in tear composition have already been described in systemic and neurological diseases. Lacrimal glands are highly innervated by cholinergic neurons, and influenced by adrenergic and dopaminergic pathways, and characteristic tear protein profiles could be detected if alterations of specific neural pathways occurred (20,21).

In two of the most frequent neurodegenerative diseases – Alzheimer's dementia (AD) and Parkinson's disease (PD) - visual impairments has already been described (22). Oxidative stress and inflammatory mechanisms could represent a common pathogenic chain in degenerative ophthalmologic and neurologic diseases, but tear abnormalities could be also linked to associated dysfunctions in autonomic nervous system. NDD are also associated with altered tear production and decrease corneal sensitivity (23).

The ocular involvement in AD affects the anterior and the posterior pole of the eye. Maintaining the integrity of visual pathways should be an important objective in assessing NDD evolution and prognosis (24). Neurodegenerative changes detected in the brain of an AD patient are presumably associated with structural changes of the neuroretina (19). Damage of the retinal neurons have been described in AD, ganglionic cell loss and optic nerve degeneration could lead to visual impairment (25,26, 27). Beta-amyloid plaques were found in the retina of AD patients from an early stage of the disease (28).

Also, beta-amyloid deposits were found in the eyes of patients with glaucoma and age-related macular degeneration, suggesting a link with AD pathogenesis (29,30). Alteration in retinal structure and blood flow impair the eye microenvironment in AD, leading to anterior pole involvement and changes in tear composition.

Lacrimal gland dysfunction has been demonstrated in AD, showing increase tear flow rate and increased protein content (9). Proteins that are differently expressed in tears of patients with AD are those involved in local defense mechanisms and eye chemical barrier, so changes in tear composition may involve a greater risk for ocular infection (9). In the tears of patients suffering from AD, lower levels of lipocalin-1, lactotransferrin, lysozyme-C, extracellular glycoprotein lacritin and prolactin-inducible protein and higher levels of dermcidin were described (9). Also, elevated levels of nucleic acid – microRNA-200b-5p were detected in the tear samples of patients with AD, compared to controls (16).

Based on these findings, a combination of four tear proteins could be used as a screening tool for AD diagnosis in asymptomatic patients: lipocalin-1, lysozyme-C, lacritin and dermcidin. Asymptomatic patients which shows a combination of these biomarkers with increased tear volume and protein content, may be considered at risk of developing AD, and may be subjects to further psychological and neuroimaging tests. These tear markers are more valuable as actually there is no tool for population screening in AD.

Visual dysfunction has already been described in PD patients, being caused by dopaminergic depletion and accumulation of a pathologic protein, alpha-synuclein, in the retina (31,32).

Tear secretion in PD patients is influenced by the specific dysfunction of autonomic nervous system. In a study, the PD patients have a decreased blink rate and tear secretion, compared to controls, complaining of dry eye sensation and blepharitis (33). The dysfunction of cholinergic pathways in PD patients influence lacrimal gland secretion, and is involved in changing tear composition.

The tears of patients with Parkinson's disease (PD) contain biomarkers that can be directly tested. High levels of tumor necrosis factor alpha (TNF- α), DJ-1 protein (a cysteine protease encoded by *PARK7* gene) (34), oligomeric alpha-synuclein (α -syn), and decreased levels of total α -syn have been described in tear fluid of parkinsonian patients (8,21).

Alpha-synuclein is the main abnormal protein identified in the brain of PD patients, being one of the components of Lewy bodies (35). Neurons which innervates lacrimal glands of PD patients are affected by neurodegenerative changes, and may release oligomeric α -synuclein into the tear fluid. On the other hand, rich corneal sensory innervation could be another source of oligomeric α -synuclein from ciliary nerves terminations (10).

Oligomeric α -syn is considered to be a strong biomarker for PD, especially in male patients. DJ-1 protein was also increased in the tears of male PD patients compared to controls (21).

It has been hypothesized that abnormal high levels of oligomeric α -syn in tears and other biofluids could precede the onset of clinical manifestations of PD, and could be used at a screening tool in detecting the risk of disease in asymptomatic people (21).

In amyotrophic lateral sclerosis (ALS), a severe NDD in which central and peripheral motoneurons are affected, an alteration of corneal small sensory fibers has been described, but there is no study regarding tear composition (36).

In Huntington disease, there are no clinically validated biofluid markers available for screening or outcome (37).

Conclusions

Tear analysis is an uncomplicated and easy to perform test, that can be used in the screening process of the general population for degenerative diseases. There are some evidences that tear biomarkers could predict with specificity the risk for NDD, and patients with positive tests may be further evaluated by specialists (9). As tears are the most important source of eye biomarkers, there is a strong reason for the development and validation of new and precise non-invasive tools to facilitate the early detection of neurodegenerative diseases and the prediction of their progression. Further research are needed to increase the specificity of tests and of tear biomarkers panel (38).

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The impact of the dry eye syndrome on the quality of life in elderly patients-minireview

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Abstract

Dry eye syndrome (DES) is a multifactorial surface ocular disease often seen in elderly patients with a high impact on the quality of life. There are a lot of risk factors related to DES such as older age, female gender, postmenopausal estrogen therapy, lack of omega 3-fatty acid in the diet, medication (antihistamines), connective tissue illnesses, radiation therapy, corneal refractive surgery, cataract surgery, hematopoietic stem cell transplantation, vitamin A deficiency, hepatitis C, androgen deficiency, cicatricial pemphigoid. The diagnosis of DES implies classical and emerging examinations. There are several types of DES. It is very important to establish the type because the treatment is according to the cause. The treatment is based on artificial tears, topical steroids, Cyclosporine A, lubricants, punctual plugs and Fatty acids Omega 3.

Key words: *dry eye syndrome, risk factors, type, dry eye treatment, quality of life,*

Introduction

Dry eye syndrome (DES) is a multifactorial surface ocular disease often seen in elderly patients. Lately it has become very common all over the world with a high impact on the quality of life. Some authors described the syndrome as a public health problem (1). The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II changed the old definition of DES introducing the term of loss of „homeostasis”(2) in the mechanism of appearance. Therefore, nowadays the definition of DES implies the instability and hyperosmolarity of the tear film, ocular surface damage and neurosensory abnormalities associated with the loss of „homeostasis”(3). In practice, DES is also called keratoconjunctivitis sicca or dysfunctional tear syndrome.

Epidemiology

It is estimated that all over the world there are 25-30 million patients with DES (4), with a frequency of 5 % to 34% (5). Some studies performed globally showed even a frequency of 50%.(2). In United States the frequency of the illness is almost 17% (6) but in Korea, Taiwan and Japan is 30% (7,8,9,10). In women, the prevalence increased with the onset of

menopausal period (5). In general, the prevalence raised with the age being 18.6% in patients older than 75 years (3,11) and women are 50% more likely to develop DES comparative with man (11). Almost 20% of patients with rheumatoid polyarthritis developed DES (12,13).

Risk Factors

There are a lot of risk factors related to DES. The American Academy of Ophthalmology revealed as mostly consistent risk factors the following: the older age, female gender, postmenopausal estrogen therapy, lack of omega 3-fatty acid in the diet, medication (antihistamines), connective tissue illnesses, radiation therapy, corneal refractive surgery, cataract surgery, hematopoietic stem cell transplantation, vitamin A deficiency, hepatitis C, androgen deficiency, cicatricial pemphigoid (6). Mark et al suggested as risk factors: the Asian ethnicity, medication (beta blockers, diuretics, tricyclic antidepressants, Parkinson medication), diabetes mellitus, human immunodeficiency virus, systemic chemotherapy, sarcoidosis, ovarian dysfunction (14). Other studies found that oral cavity cancer, chronic fatigue syndrome,

Helicobacter Pylori were associated with DES (15,16). Particularly in elderly patients the autoimmune rheumatic disease represent a risk factor for DES, such as: Sjogren syndrome, rheumatoid polyarthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis and polymyositis (17,14). A study from Taiwan revealed that high temperature, carbon monoxide and nitrogen dioxide were strongly associated with DES (18,19). On the other hand the use of glaucoma medication, asthma, fibromyalgia and presbyopia were considered by some studies risk factors in the appearance of DES (20,21,22). Some authors suggest that staring for a long time at computer screens induce a decreased blink rate with the development of DES (14).

Pathophysiology

The anatomical structure of the tear film consists in three layers. The inner mucin layer is composed of gel and soluble mucins produced by specialized conjunctival goblet cells that adhere the tear film to epithelial cells. It facilitates the aqueous layer to extent uniformly over cornea (23). The middle layer is the aqueous layer secreted by lacrimal and accessory glands to offer eye hydration and lubrication and helps in the removal of foreign bodies (24). The outer lipid layer produced by Meibomian and Zeiss glands to reduce tear evaporation (25,26,27). Cher et al (28) proposed a two-tiered model in which the mucin and aqueous interact in a muco-aqueous layer. Georgiev et al (29) showed that lipids produced from the Meibomian glands cannot inhibit the rate of evaporation. Moreover there are some studies that revealed other functions of the outer lipid layer such as: spreading the tears between blinking, providing a low surface tension for tear film and viscoelasticity properties (30,31,32). Tear production is under the control of sympathetic and parasympathetic stimulation of the lacrimal glands, which in turn is controlled by a neural reflex arc coming from the ocular surface (33). Cox et al (34) consider that the innervation of the Meibomian glands and goblet cells is also under parasympathetic control. The conjunctival epithelium includes immune cells such as natural killer, dendritic cells, macrophages, CD4+ and CD8+ T cells antimicrobial defense but also in DES. All these layers associated with the innervation provide tear film stability. Therefore, every factor which can influence the stability may induce DES as

a consequence of disruption of the lacrimal functional unit composed by all the structures implicated in the ocular surface. During last years, the pathophysiology of DES has experienced a real change. Several studies showed that inflammation is another major factor implicated in DES mediated by the lymphocytes T within the conjunctiva (35,36,37,38).

The risk factors may induce tear hyperosmolarity which is the trigger for the pro-inflammatory effect on the ocular surface epithelium, by activating stress signaling pathways, increase the inflammatory mediators (cytokines, chemokines and matrix metalloproteinases) and the CD4+ T cells. The result will be the barrier disruption, neural sensitization, glandular secretion disfunction and apoptosis, including goblet cells. As a consequence, will appear tear instability and surface desiccation (39). All these inflammatory mediators upregulate each other, increasing the inflammatory cascade. There are studies which revealed increased level of inflammatory mediators in other ocular surface disease (atopic and vernal keratoconjunctivitis, keratoconus, recurrent corneal erosions, ocular burns) (40,41,42,43,44,45).

Clinical features

Conceding the severity of DES, the patient may complain of mild or episodic discomfort to severe and constant symptoms associated with visual symptoms such as: burning sensation, itchy eyes, aching sensations, heavy eyes, fatigued eyes, sore eyes, dryness sensation, red eyes, photophobia and blurred vision. Another common symptom is something called a foreign body sensation — the feeling that grit or some other object or material is "in" the eye. Surprisingly, the patients can have watery eyes because dryness on the eye's surface sometimes will over-stimulate production of the watery component of your tears as a protective mechanism. But this "reflex tearing" does not stay on the eye long enough to correct the underlying dry eye condition. In addition to these symptoms, dry eyes can cause inflammation and (sometimes permanent) damage to the surface of the eye.

Slit lamp examination will reveal increased thickness of the free palpebral margin and the obstruction of Meibomian glands orifices with solid granulose material. The inflammation of the Meibomian glands (meibomitis) and of the free margin (blepharitis) may be part of the clinical aspect (5). In advanced stages may appear

conjunctival and corneal scars, phylamentous keratitis, recurrent corneal erosions, corneal ulceration and even corneal perforation.

Dry eye examination

Clinical features and the impact on life quality require a correct examination of the dry eye. Classical and emerging examinations are able to confirm a positive diagnosis of dry eye.

Classical examination

[1] Epithelial staining

Fluoresceine, Bengal Rose or Green Lissamine can be used as a staining dye in order to establish ocular surface anomalies, tear film quality or dry eye severity (46). Fluorescein is the most frequent dye used in the evaluation of dry eye. It is useful to identify corneal epithelial defects at which level cornea will stain. The staining can show different aspects characteristic of dry eye especially in elderly patients. Bengal Rose is best to be used as an adjunct dye because of its lack of sensitivity and specificity (47). Machado et al (48) showed that Bengal Rose is toxic for the cornea that is why is seldom used and that Green Lissamine is not toxic for the cornea and has a better tolerability.

[2] Schirmer test

It is the most widely used test for evaluating dry eye. Even though the test is irritative, invasive and in some cases unreliable. This may induce a high risk of underdiagnosis of dry eye (49,50). The test gives information about tear production. There are two tests, Schirmer I (with or without anesthesia) and Schirmer II which only measures reflex tears comparative with the first one which measures total tear secretion. Normal test values vary from 8 mm to 33 mm but is considered normal value greater than 10mm (51,52). Lin et al (52) revealed that much more reliable results seems to offer the Schirmer test without anesthesia.

[3] Fluorescein clearance test

The test offers information about tear secretion and drainage. It combines Schirmer test with the use of proparacaine and 5µL of Fluorescein® (0.25% fluorescein with 0.4% benoxinate hydrochloride). A normal value is considered to be equal or more than 3 mm at the first 10-minute interval. The disadvantages of the test consist in the fact that is time-consuming, irritating, and not reproducible (53).

d. Tear break-up time

The test measures stability of the tear film. It is performed at slit lamp, by instillation of fluorescein

in the conjunctival inferior fornix and asking the patient not to blink. The positive diagnosis of dry eye is confirmed if a dry area appears before 10 seconds (54). Vanley et al (54) demonstrated that it is a quick test, is unexpansive but is not reproducible and it is inaccurate.

Emerging examinations

• Reflective meniscometry

Is a noninvasive technique giving quantitative information about tear meniscus curvature (19). The exam needs a portable slit-lamp mounted digital meniscometer. Yokoi et al (55) showed that the results are similar to those obtained by ocular coherence tomography (OCT).

b. Ocular coherence tomography

Is a noninvasive technique to measure the meniscus height. Savini et al (56) showed that tear meniscus height was found to be significantly lower in dry eye patients compared with controls using ocular coherence tomography (OCT.) Messner et al (57) revealed that a major advantage of OCT is the capacity to measure tear film thickness. One study found highly reproducible measurements using ultrahigh resolution OCT (57). Werkmeister et al (57) revealed that the normal value of central tear film thickness was $4.79 \pm 0.88 \mu\text{m}$.

c. Tear normalization test

Is a simple, inexpensive and noninvasive test. It consists in the examination of visual acuity before and after the instillation of no viscous artificial tears drops based on the fact that this kind of drops improve temporary the visual acuity in DES (58).

[4] Biomarkers

Analyzing tear biomarkers in order to establish the diagnosis of dry eye gained a lot of popularity lately. High level of inflammatory biomarkers, especially matrix metalloproteinase 9 suggest the presence of DES (59,60). Furthermore, allergy biomarkers such as lactoferrin and immunoglobulin E in the tear film will be very useful in the diagnosis of dry eye. Lee et al (61) showed high level of cytokine (interleukin-17, interleukin-6, and tumor necrosis factor-alpha) in patients with dry eye and Sjogren syndrome compared with patients with dry eye without Sjogren syndrome and controls.

[5] Tear osmolarity

Is a technique used to quantify osmolarity and be useful in the diagnosis of dry eye. Versura et al (62) demonstrated that patients with dry eye have a high level of tear osmolarity as a result of the ocular surface damage and inflammation. In dry eyes the osmolarity value is higher than 308 mOsm/L.

[6] Ocular Surface Thermographer

It is a device in order to measure the tear film temperature based on the fact that diurnal changes in corneal temperature may indicate ocular surface abnormality or corneal pathology.[63]

Types of Dry eye

DES can be caused by deficient tear production or by increased evaporative loss. Both groups can be divided into several types: lipid anomaly dry eye, allergic and toxic dry eye, cicatricial condition, autoimmune condition, lid surfacing anomalies and marginal dry eye.

Lipid anomaly dry eye

Lipid anomaly dry eye is an evaporative DES and appears as a result of Meibomian gland dysfunction (64). Is the most frequent type.

Aqueous Tear deficiency

Aqueous Tear deficiency is the result of multiple causes linked with autoimmune diseases.: Sjogren syndrome and cicatricial pemphigoid. Sjogren syndrome is an autoimmune disease associated with lacrimal and salivary gland lymphocytic infiltration with T cell, B cell, dendritic and natural killer cells (65). In elderly patients we often diagnose this syndrome. Cicatricial pemphigoid is another autoimmune disease which is associated with dry eye, loss of vision and conjunctival vascularization. Dart et al (66) and McCluskey et al (67) demonstrated that in this type of DSE the treatment has to control the conjunctival inflammation combined with general administration of steroids or methotrexate, infliximab or intravenous immunoglobulin therapy.

Allergic and toxic dry eye

Is the form of DES related with allergy or toxin. The main cause is allergic conjunctivitis that is why this form may appear also in pediatric patients (68,69).

Cicatricial condition dry eye

This form of DES has two common causal entities: xerophthalmia and trachoma. Both diseases appear in urban areas where the patients have poor hygiene, low level of life or improper administration of A vitamin (70,71).

Blinking anomalies

Is caused by reduced or incomplete blinking. Is often present at persons who stay in front of the computer or watching TV for several hours, especially in elderly patients. Ousler et al (72) showed that in dry eye patients rate of blinking was shorter comparative with the normal ones.

Marginal dry eye

Appears in patients who have a normal tear function only in some condition. So, in improper conditions (air conditioning, contact lenses use, alcohol ingestion) the lacrimal film may be damaged (73).

Dry eye treatment

The purpose of the treatment is to improve the comfort of the patient and quality of life and to regain the ocular surface homeostasis (74). Several treatments were proposed during last years according the type of DSE, clinical features and causal mechanism. Additionally, it is mandatory to treat Meibomian gland dysfunction and the systemic causal illness.

Artificial tears

Artificial tears were by far the most used drugs for several years, providing tear stability, less ocular stress and contrast sensitivity (19). An important progress in the evolution of artificial tears was the elimination of Benzalkonium chloride (BAK) the common preservative used in eye drops and which was responsible for the ocular surface damage. There are studies which showed that osmolarity balanced artificial tears (carboxymethylcellulose sodium) were the preferred treatment in patients with moderate to severe dry eye and liposomal spray for patients with lipid layer deficiency (75,76). Single-dose application units is preferred in case of DES to prevent the possible contamination. This is very important in elderly people because many of them have glaucoma with antiglaucomatous drugs as treatment.

Autologous serum eye drops

Higuchi et al (77) and Geerling et al (78) revealed the efficiency of autologous serum eye drops in the treatment of dry eye. It is created from human serum which contains cytokines, fibronectin, epidermal growth factor, vitamin A, substances whose role in maintaining the integrity of corneal and conjunctival epithelium is very well known (79).

Cyclosporine A

The effect of Cyclosporine A is to restore the ocular surface by stopping the T cell activation pathway and decreasing the cytokine level and increasing the Goblet cells number in corneal epithelium (80). You-Kai et al (19) and Straub et al (81) showed a real improvement after twice daily administration.

Punctum plug

The obstruction of the lacrimal punctum with plugs is another way to prolog the lubricants effects and conserve natural tear (82).

Anti-inflammatory agents (steroids)

De Paiva et al (83) demonstrated that the steroids and Doxycycline suppress the activity of metalloproteins and inflammatory cytokines from the ocular surface. Follow-up of the patients is very important taking into consideration the possible adverse effect of topical steroids such as glaucoma and cataract formation (84).

Fatty acids Omega 3

Nowadays, fatty acids Omega 3 are considered to be a potential progress in the treatment of DES. Liu et al (85) showed that they act directly on human Meibomian gland epithelial cells in order to improve the quality and quantity of intracellular lipids, by this inducing the tear film stability and influencing the quality life of this patients.

Conclusion

Dry eye disease is a frequent entity, especially present in elderly people. The early diagnosis and management is mandatory in order to improve the quality of life at this patients.

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An uncommon association of dry eye syndrome with relapsing polychondritis and necrotizing scleritis

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Abstract

Introduction Relapsing polychondritis (RP) is a rare disease evolving with recurrent cartilage inflammation, but also with ocular, respiratory, cardiac and vascular involvement. Associations with various autoimmune disorders and with hematological diseases, mainly leukemia, lymphoma and myelodysplastic syndrome and rarely with hemolytic anemia, have been described. We report a 63-year patient with thyroiditis and pernicious anemia in whom a left eye necrotizing scleritis led to the diagnosis of RP and common variable immune deficiency (CVID). The necrotizing scleritis was successfully operated with scleral graft. However, the disease control was difficult to be achieved with glucocorticoids and various immune suppression regimens tried (including cyclophosphamide, cyclosporine, azathioprine, leflunomide and infliximab) along with immunoglobulin substitution. The association of RP and CVID or CVID-like diseases is rare, another 4 cases having been reported. We review the literature and discuss the diagnostic and management difficulties. A multidisciplinary team approach is necessary in this setting.

Key words: *relapsing polychondritis, dry eye, necrotizing scleritis,*

Introduction

Necrotizing scleritis is a severe ocular complication of systemic diseases, that may rarely be inaugural. Necrotizing scleritis may occur in other diseases such as rheumatoid arthritis, in systemic vasculitis as granulomatosis with polyangiitis, Crohn's disease, relapsing polychondritis (RP) etc. Relapsing polychondritis (RP) is a rare disease evolving with recurrent cartilage inflammation, but also with ocular, respiratory, cardiac and vascular involvement. Associations of RP with various autoimmune disorders and hematological diseases, mainly leukemia, lymphoma and myelodysplastic syndrome and rarely with hemolytic anemia, have been described (1).

Common variable immune deficiency (CVID) is a rare disease manifesting with low concentrations of immunoglobulins, mainly IgG and IgA, and with inefficient production of antibodies to different pathogens (2). Autoimmune diseases, including thyroiditis, pernicious anemia, rheumatoid arthritis and rarely RP, are associated in 20% of cases (2).

Case report

A 63-year female patient with a 6- year history of autoimmune thyroiditis and hypothyroidism, with pernicious anemia since 2 years, two episodes of red eye in the last 2 years, on chronic substitutive

therapy with L-thyroxine, vitamin B12 and folic acid, with bronchial asthma and several episodes of pneumonia in the last 2 years, presented in the Emergency for a red painful left eye. She also complained of chronic hoarseness, non-productive cough and episodic joint pain. Family history revealed that her mother suffered from asthma and Basedow-Graves' disease and her sister was diagnosed with Hashimoto thyroiditis.

The general clinical exam was normal.

The functional ocular examination revealed a best corrected visual acuity (BCVA) of 0.9 at right eye (RE) and 0.2 at left eye (LE). Ocular refraction was -3.50 sf/ cyl -0.75 ax10° and -2.00 sf/cyl -2.25 ax100°. The intraocular pressure in the RE was 17 mmHg and 59 mmHg in the LE, measured by Goldmann aplanotometry. The pupillary reflex at light was present in both eyes and was normal. The Schirmer test was normal for the RE and 4 mm for the LE. The break-up time (BUT) was 5 seconds, revealing a great instability of tear film. Corneal and conjunctival staining was grade III on the Oxford Grading. (Table 1)

The slit lamp examination showed a normal examination in the RE. Left eye presented a necrotizing area of 2.5/1 cm in the superior

perilimbal region with scleral and conjunctival necrosis, localized at about 1 cm from the limbus with ciliary body visibility covered with mucus secretion. At the same eye, cornea was transparent with a thin white perilimbal infiltration, a medium sized anterior chamber, ptosis and edema of the superior eyelid. (Fig.1)

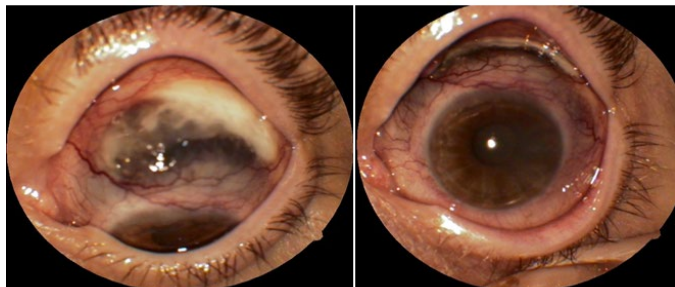


Fig. 1. The slit lamp examination - a necrotizing area of 2.5/1 cm in the superior perilimbal region with scleral and conjunctival necrosis at about 1 cm from the limbus with ciliary body visibility

Table 1. The evaluation of the dry eye syndrome

Schirmer Test		BUT (Break - up time)		OSDI (Ocular Surface Disease Index)
RE	LE	RE	LE	OSDI = 35
normal	4 mm	normal	5 seconds	

Ptosis diagnosis was done by measuring the distance between the lid margin of the upper eyelid and corneal reflex RE= 4 mm / LE =1mm (4.5). The distance between the lid margin of both eyelids was RE=11 mm /LE =8mm (8-12), the superior rectus muscle function was RE= 7mm/ LE =7mm (12-15). The distance between the lid margin and the orbital margin of the upper eyelid was RE =10mm/ LE =10mm (10). Fundus examination revealed retinal angiosclerosis in both eyes.

An ocular ultrasound examination was performed, showing a thickening of the superior rectus muscle (tennonitis) with severe thinning of the ocular sclera (about 0,5 mm) in the superior area of the ciliary body. (Fig.2)

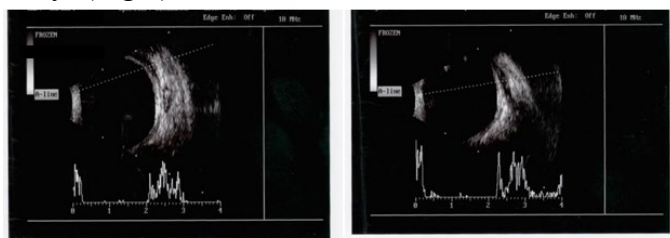


Fig. 2. Ultrasound exam at left eye – Thickening of the superior rectus muscle and thinning of the sclera in the superior area.

The screening for infection was negative (negative conjunctival secretion cultures, pharyngeal swab,

bronchial secretion, hemocultures, procalcitonin, Mycoplasma, Cytomegalovirus, Epstein-Barr, hepatitis B and C, HIV). Examination revealed a deformed ear cartilage. A relapsing polychondritis was suspected, soon confirmed by the presence of florid ear chondritis. (Fig.3)

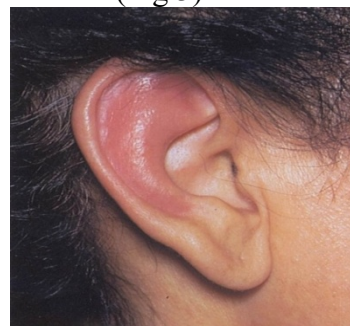


Fig. 3. Ear chondritis

Laboratory revealed an elevated ESR (85 mm/h) and CRP (2.4 mg/dL, normal<0.6 mg/dL). C3 and C4 were normal (C3 138, normal 60-150 mg/dL, C4 18, normal 16-35 mg/dL). Antinuclear, anti-Ro, anti-La, anti-neutrophil cytoplasm, anticardiolipin and anti-beta-2 glycoprotein antibodies were negative, but the anti-parietal gastric cell antibodies were positive in immunofluorescence (1/80) and the anti-TPO antibodies were positive (625 IU/mL, normal <45 IU/mL). There was a moderate anemia (Hb 8.7), with minimal hemolysis (indirect bilirubin 1,2 mg/dL, normal<1 mg/dL), LDH 512 (normal 230-460IU/L), with normal WBC with differential and platelet count (5400/mm³ and 217 000/mm³ respectively). The vitamin B12 (2 years previously low, 125 pg./dL, normal >210 pg./dL) and folic acid were normal under substitution, as were the T3, T4 and TSH values. Direct and indirect Coombs test were negative. The immunogram, however, repeatedly revealed low immunoglobulin titers, suggestive of common variable immunodeficiency (IgG 42 IU/mL, normal 90-120, an IgA of 61 (normal 60-240) and a normal IgM (158, normal 70-250 IU/mL). The urinary Bence-Jones proteins, the immunoelectrophoretic with immune fixation of the blood and urine for free light immunoglobulin chains was negative. Due to the low value of hemoglobin (5,6 g/dL), we suspected anemia and a hematologic consultation was performed, showing VEM: 112fl, reticulocytes =1‰, discrete leucopenia - WBC=3100/mm³, neutropenia, neutrophil 1350/mm³, discrete thrombocytopenia, PLT=120 000/mm³, blood smear: huge erythrocytes, hyper segmented neutrophils. The myelogram showed the presence of megaloblastic cells with giant metamyelocytes; there were no elements of

dysplasia on the granulocytic and megakaryocytic series. The bone marrow aspirate examination revealed megaloblastic cells with giant metamyelocytes with some myelodysplastic changes. (Fig.4) The patient refused the iliac bone biopsy. A gastroscopy revealed atrophic gastritis, and the rest of malignancy screening (thyroid and abdominal ultrasonography, chest CT, mammography, gynecological examination with PAP smear) was negative as well.

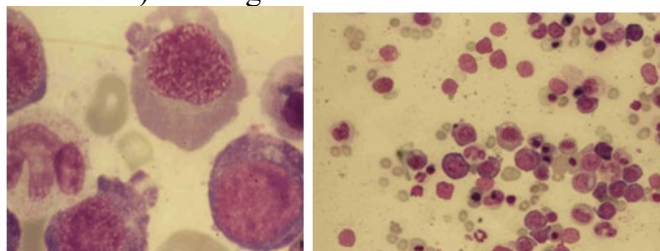


Fig. 4. Bone marrow examination – Megaloblastic cells with giant metamyelocytes

In order to confirm the polychondritis a PET –CT scan was done, which emphasized the active disease in the joints of the patient. (Fig.5)

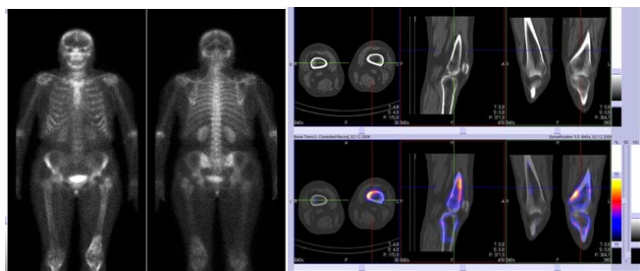


Fig. 5. Whole body PET – CT Scan – and knee section of PET-CT scan – activity of the polychondritis.

Final diagnosis was at both eyes: direct compound myopic stigmatism and at LE necrotizing scleritis, pseudoptosis, secondary glaucoma and severe dry eye syndrome, relapsing polychondritis, common variable immune deficiency, megaloblastic anemia, autoimmune thyroiditis.

Scleritis differential diagnosis was made with anterior scleritis, purulent scleritis, scleromalacia perforans, blue scleral syndrome, ciliary body malignant taking in consideration the age, gender, clinical and paraclinical examination and causative factors.

The purpose of the treatment was to diminish the local inflammation, to decrease the intraocular pressure and to cover the wall defect and prevent the development of new necrosis. The patient was treated topical with a fixed combination of anti-inflammatory drugs and antibiotics: Tobramycin

3mg with Dexamethasone 1 mg, 5 gut/day, Ofloxacin 0,3%, 3 gut/day, Tropicamide 1%, 3 gut/day and antiglaucomatous treatment with Timolol 0,5%, 2 gut/day. For the dry eye syndrome was indicated Cyclosporin 1 mg 1 gtt/day and artificial tears. The patient was treated surgically after signing a surgical consent. It was performed a scleral and conjunctival plasty with a scleral graft recruited from the RE with the acceptance of the patient. Also, systemic therapy with methylprednisolone pulses (1g/day iv for 3 days, then 1 mg/kg/day orally one month with tapering), and cyclophosphamide monthly iv pulses of 15 mg/kg, 6 pulses, cyclosporine – stopped due to severe hypertension and renal insufficiency, azathioprine – stopped due to intolerance, then cyclophosphamide orally. The visual acuity and intraocular pressure returned to normal and she had less episodes of auricular and respiratory chondritis, but persistence of severe episodic arthritis. (Fig.6)

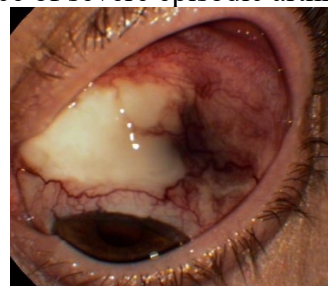


Fig. 6. – Postop follow-up – integrated scleral graft

She also received intravenous immunoglobulin monthly substitution (0.4 g/kg/month). However, while on immunosuppression therapy, two years after the first episode of necrotizing scleritis, she developed another similar episode, in the same eye. The cerebral MRI and the repeated workup for vasculitis (ANCA, ANA, C3, C4, cryoglobulins) were negative. Methylprednisolone and cyclophosphamide pulses were restarted. Due to the incomplete disease control, a course of high-dose immunoglobulins (0.4 g/kg for 5 days) was given, with ocular improvement, but minimal alleviation of joint symptoms. She developed tibiae-tarsal and subtalar bilateral arthritis evolving to dissecting osteochondritis. Leflunomide 20 mg/day and a single infusion of infliximab 3 mg/kg were given, stopped because of prolonged diarrhea revealing an E. coli sepsis. She was transferred to the Infectious disease department, where after imipenem and ciprofloxacin the hemocultures and stool cultures became negative and the general status improved. Echocardiography did not show valvular

vegetations, nor cordage papillary dysfunctions or thoracic aorta aneurysms. However, arthritis was severe, and she developed florid nasal and laryngeal chondritis. She was continued on low-dose glucocorticoids and leflunomide 10 mg/day, along with immunoglobulins. When she did not show up for the regular admission, we found out that she had a non resuscitable cardio-respiratory arrest, and no autopsy was performed, at family's wish.

Discussions

RP polychondritis is a rare disease involving mostly the cartilage. The McAdam criteria required for diagnosis include auricular chondritis, nasal chondritis, non-erosive inflammatory polyarthritis, ocular inflammation, laryngo-tracheal involvement, and audio-vestibular dysfunction (3). RP is associated with hematological pathology. RP is strongly associated with myelodysplastic syndrome (MDS) (4). MDS are clonal disorders of hematopoiesis characterized by peripheral cytopenia and a dysplastic bone marrow, usually hypercellular (5-50% erythroid precursors in the marrow) (5). Although suggestive for an MDS, our patient did not have enough diagnostic criteria, and she refused medullar biopsy. The megaloblastic anemia was attributed to pernicious anemia, in the context of antiparietal gastric cell antibodies and low vitamin B12. The differential diagnosis between MDS and pernicious anemia solely on bone marrow biopsy is difficult (6,7,8). Although in the assessment of a megaloblastic anemia a MDS and a pernicious anemia are considered mutually exclusive, they may rarely co-exist (8,9,10). Moreover, pernicious anemia may mimic MDS when falsely normal vitamin B12 levels are found, in the presence of anti-intrinsic factor antibodies (11). A nonrandom 7q- chromosomal abnormality has been observed in cases of severe vitamin B12 and folate deficiency (12). In our patient cytogenetic studies have not been performed.

Common variable immune deficiency (CVID) is a rare immune deficiency characterized by low levels of serum levels of IgG, IgA and often IgM and reduced or absent antibody production after exposure to pathogens (2,13). The serum IgG is always reduced, generally less than 400 mg/dL. The disease is often diagnosed in adults between 20-40 yrs., although it may present in children and older adults as well (2). Most CVID patients can be classified in 2 groups by diseases phenotypes that are stable in time: predominantly with infection, or with infection and predominantly

inflammatory/autoimmune conditions (2). Autoimmune diseases appear in up to 20% of patients (14) including thyroiditis and pernicious anemia (13,15). CVID and other primary B cell immunodeficiencies, such as protein C kinase delta deficiency, with a CVID-like picture, have been rarely associated with RP (Table 2).

Ocular inflammation is present in 2/3 of patients with RP (4). Scleritis may be the sole manifestation of RP but rarely is an inaugural sign. (16,17). In CVID, uveitis was found in 1.6% of cases, generally chronic, bilateral and often granulomatous, sarcoid-like (18). Other ocular types of involvement reported are keratoconjunctivitis, retinal vasculitis and retinal vein occlusion (19). Keratitis may be infectious and/or inflammatory (19). Bilateral consecutive sterile central corneal perforations were reported in a CVID patient, responsive to topical glucocorticoids. (20). However, patients with CVID may develop ocular infections even while on iv Ig substitution and without the typical clinical picture of infection (19).

Both RP and CVID are associated with decreased life expectancy, often through association of a hematologic malignancy (2,14). The median age of death in a series followed up for 4 decades was 44 years for females and 42 years for males, due to respiratory failure from chronic lung disease, lymphoid or other malignancy or infections, much higher in patients with inflammatory complications than in those with infection only (14). Lymphomas in CVID are more commonly extra nodal and appear in unusual locations, such as lungs or mucosal-associated lymphoid tissue (2). In our case the direct cause of death could not be established as the autopsy was not permitted, but no malignancies were apparent at the initial screening.

To our knowledge, the case is unique in the presence of recurrent necrotizing scleritis with secondary glaucoma, dry eye syndrome and of the common variable immune deficiency associated with a pernicious anemia. This association is clinically challenging. It is possible that the cytokines from tear film as a mark of the inflammation associated with dry eye could increase the local inflammation. (21,22,23,24,25,26). Nevertheless, Ciclosporin was recommended as a local immunosuppressant agent which blocks the activity of T cells combined with artificial tears to supply the deficit. The diagnosis of RP in CVID may be delayed in the absence of characteristic ear chondritis, as respiratory involvement and bronchiectasis may be found in

Pt no		Age of CVID dg	Age of RP diagnosis		Reference
1 (?)	Recurrent otitis media, auricular chondritis bilateral, polyarthritis	15 mo	4 years	Methotrexate, NSAIDs, Ig iv substitution	Karaca et al, 2009 (Int J Dermatol)(15)
2 (M)	23-year male, RP (auricular chondritis, costal chondritis, bronchomalacia) esophagus-like bronchus	23 yrs	23 yrs	Prednisone 60 mg/day	Zhao et al, 2016(5)
3 (M)	14-yrs, ear chondritis, epiglottitis, costovertebral and TT joint *decreasing IgG2		14 yrs	Steroids, methotrexate, Ig iv monthly	Goldman et al, 2015(12)
4 (M)	Nephrotic syndrome, membranous GN, RP, hypothyroidism, antiphospholipid syndrome (aseptic endocarditis, pulmonary thromboembolism) *PRKCD mutation	15 mo	>3 years	Low-dose steroid, anticoagulation, IG substitution, anti-CD20 (2 courses), MMF	Salzer E et al, 2016(24)
PRKCD – protein C kinase delta; * CVID-like syndrome					

Table 2. Table 1: CVID and CVID-like diseases in RP

both. Moreover, the commonly found splenomegaly and adenomegaly may mislead with regard to a hematological malignancy often associated to RP. Another pitfall is granuloma finding on tissue biopsies in CVID, that may lead to confusion with polyangiitis with granulomatosis in the presence of chondritis (13). The dramatic sight-threatening ocular involvement always needs an urgent intervention and a balance between the immunosuppression-associated benefits and risks, in the presence of immunodeficiency. When a certain manifestation is alleviated by immunoglobulin substitution, an infectious etiology is more likely (13). Nevertheless, severe immunosuppression is often complicated by infections, even under immunoglobulins substitution, like in our case. Also, cyclophosphamide may not prevent the development of recurrent necrotizing scleritis. Anti-TNF agents have been used successfully in necrotizing scleritis complicating RP, and also with improvement in granulomatous diseases in CVID (13); however, in our case, despite ocular involvement alleviation, a single dose was complicated by an E coli sepsis. Rituximab, an anti-CD 20 antibody, is a logical and very useful alternative (2), although not universally successful (27,28). The association of RP with CVID requires frequent consultations and a multidisciplinary team approach.

Declaration of conflict of interests/Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Informed consent

Informed consent was obtained from the patient included in this study.

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Adherence to CPAP Therapy - a necessity in the Pulmonary Rehabilitation of patients with Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) has become a major worldwide health concern and affects 2-4% of males and 1-2% females. In subjects diagnosed with mild or severe OSA, CPAP (Continuous Positive Airway Pressure) is highly efficacious in improving the specific quality of life and the cardiovascular outcome but adherence to treatment limits its overall effectiveness. Factors that influence the adherence to CPAP therapy include patients' individual characteristics, disease severity, titration procedures, the presents of side effects and the psychosocial factors. The management of this pathology is multidimensional and is based on some interventions such as lifestyle modifications, physical training, oral appliance and educational, pharmacological, technological strategies. These measures are implemented to limit the adverse effects of CPAP therapy in order to maximize the CPAP usage and to obtain a decrease of symptomatology and an optimum quality of life in OSA patients.

Key words: CPAP adherence, obstructive sleep apnea, pulmonary rehabilitation,

Introduction

Obstructive sleep apnoea (OSA) is a prevalent disorder that has become a major worldwide health concern. It is characterized by episodes of periodic collapse of the upper airway during sleep caused by anatomical modifications and a decrease of pharyngeal dilator muscle tone (1).

In more than 60% of patients OSA is associated with obesity, being responsible for daytime sleepiness, reduced quality of life, increased risk of motor vehicle accidents, cardiovascular and metabolic disease, impacting the healthcare use and mortality (2,3,4).

OSA affects 2-4% of males and 1-2% females but the last category seems to be underdiagnosed due to atypical symptoms such as fatigue, morning headaches, insomnia with less witnessed sleep apneas. Recent studies showed that 6% of women and 13% of men had moderate to severe sleep apnea that correlates with a large increased risk of all-cause mortality through cardiac arrhythmias, pulmonary and systemic hypertension, stroke, insulin resistance, myocardial infarction and road accidents (5,6,7).

Continuous Positive Pressure (CPAP) Therapy

In accordance to international guidelines CPAP is recognized as the gold standard treatment in cases of moderate to severe OSA (5).

CPAP was first discovered in the 1980s and its role is to provide a continuous mild air pressure in order

to maintain the airway open and to prevent the collapse or the obstruction. The system include a CPAP machine capable to create the pressure gradient, tubing and CPAP mask. In the case of OSA, the preferred CPAP mask it only covers the nose but also, in selected cases, can cover the nose and the mouth (5).

In patients with moderate or severe OSA (AHI \geq 15 events/hour of sleep), CPAP therapy is indicated, independently from the severity of symptoms or diagnosis of comorbidities. In cases of mild OSA, (AHI is above 5 and below 15) CPAP is indicated if the subjects associate other comorbidities, such as hypertension, coronary artery disease, or previous cerebrovascular accidents, or in the presence of other symptoms (i.e., sleepiness, impaired cognition, mood disorders). Alternative options include weight control, oral appliance, oropharyngeal exercises, mandibular advancement devices, upper airway stimulation and a number of upper airway surgical approaches (8).

CPAP is capable of improving the symptomatology such as snoring, choking, nocturia, daytime somnolence and the lack of memory or concentration. Beside this, CPAP is considered to improve specific quality of life and minimize the cardiovascular risk by reducing the blood pressure and the systemic inflammation. A very important factor in CPAP therapy is the patient compliance,

mostly because poor adherence limits treatment efficacy (5, 9).

Compliance has been defined as usage of CPAP machine more than 4 hours per night for more than 70% of nights. In the literature, adherence rates range from 40-85% but there is no specific threshold that guarantee that efficacy is absolute (10,11). So, recent studies has stipulated that the greater the use of CPAP machines the better the results of the outcomes (5).

However CPAP therapy is associated with some side effects including dermatitis, epistaxis, rhinitis, nasal congestion, mask leak, barotrauma, aerophagia and claustrophobia, that must be controlled in order to obtain optimum compliance (5).

Exploring the Concept of a “Dose-Response” Relationship between Adherence and Outcomes

Taking into account the relationship between CPAP usage and outcomes, the term “dose” it refers to hours of usage per night more than pressure setting. This parameter should be established according to habitual sleep duration of each subject, level of impairment and the sensitivity of each outcome measure. The clinicians must remember that the CPAP usage time is not the same thing as total sleep time. For clinicians identifying ways to increase CPAP compliance is a major challenge mostly because OSA has an impact on cognition, work place performance, sleepiness, mood, functional status and driving ability, aspects that can be improved by CPAP treatment (12).

Optimal Adherence for Controlling Daytime Symptoms

The recent literature in this domain claims that the clinician should establish an individualized usage level, taking into account the outcome of CPAP treatment. Weaver et al. suggested in an uncontrolled study including 149 subjects diagnosed with severe OSA that the amelioration of symptoms occurred at different usage level: objective sleepiness at 6 h CPAP therapy per night, self reported sleepiness at 4 h therapy per night and functional status at 7,5 h per night (13). In another study Antic et al. observed an improvement in subjective sleepiness in those wearing CPAP more than 5 h per night and the normalization of objective sleepiness in those wearing CPAP more than 7 h per night (14). Beside this, in patients which associate cognitive and memory impairment it was seen an

amelioration of symptoms in patients with a usage of 5,2 h of CPAP therapy per night (15).

Optimal Adherence for Controlling Cardiovascular Symptoms

In the last decades there are more evidences that suggest that greather CPAP use is responsible for improvements of cardiovascular outcomes. Barbe et al. developed a study including 359 subjects diagnosed with OSA and hypertension which do not associate excessive daytime sleepiness and concluded that the reduction of blood pressure (BP) was more evident in patients with an adherence more than 5,6 h per night (16). Even if the normalization of BP can be cofounded by other factors (greater adherence to antihypertensive medication, lifestyle modifications), a meta-analyses conducted by Haentjens et al. stipulated that there is a reduction in mean BP of 1.4mmHg with each 1h improvement in CPAP compliance with direct effects on cardiovascular morbidity and mortality compared with subjects with nonadherence (17).

These improvements were better observed in patients with OSA, excessive daytime sleepiness and arterial hypertension. Montesi et al. noticed a reduction of 1.9mmHg of the systolic values of BP and of 1.4mmHg of the diastolic BP in patients with a higher CPAP compliance which have a 5 point reduction of the baseline Epworth sleepiness scale (18). Since the peaks of higher BP occurs at the termination of obstructive respiratory events, the main role of CPAP is to reduce the arousals and the baseline sleepiness and to improve the sleep quality, that is why the adherence to therapy is very important (12).

Factors That Influence or Predict CPAP Use

In literature there are a lot of studies that summarize the factors that can influence or predict CPAP use, which can clarify the patients' decision to adhere to CPAP treatment.

Disease and patients characteristics

First of all, disease severity measured by apnea-hypopnea index, oxygen desaturations and symptomatology (excessive daytime sleepiness-EDS) are the influential factors that contribute to the CPAP adherence. In these conditions the delivery of CPAP must take into account the patency of upper airway structures moreover because a decrease in nasal volume is responsible for nasal resistance which influence the CPAP use (19).

Lee et al. proved that patients with a smaller nasal cross sectional area and a decreased nasal cavity volume had a lower CPAP adherence. In another study conducted by Morris et al., OSA patients with various degrees of obstruction at the inferior turbinate were observed for 18 months (20). From those, 48% had a lower compliance to CPAP therapy and the majority of subjects were not using at all CPAP after 18 months. So, it was stipulated that acoustic rhinometry has a high sensitivity and specificity and is capable to exclude the patients with CPAP intolerance. It was recommended that all OSA patients perform an acoustic rhinometry measure at baseline and after 3 months of CPAP therapy (19).

The nasal resistance may influence the initial acceptance of CPAP, so Sugiura et al. concluded that the odds of rejecting CPAP were almost 50% greater for every increase of 0,1 Pa/cm³/s. So, nasal anatomy may have an influence on CPAP adherence, but not necessarily subjective nasal complaints (21).

Other factors that influence CPAP compliance are depression and low mood at the diagnosis moment, by altering the perception of symptoms and the experience of side effects. Wells et al. concluded that by controlling depressive symptoms of patients which require CPAP treatment, the clinicians can achieve a better improvement in daytime symptoms associated with OSA (22). Brostrom et al. showed that OSA subjects which associate a personality type of social inhibition and negative affectivity had low adherence to CPAP treatment (23).

Another well known factor implicated in the development of OSA and another respiratory disease is smoking, but its role is controversial in literature. At first sight nicotine decrease the upper airway resistance with a consequent reduction in the risk of OSA. In case of withdrawal, this resistance would become more important and would cause a greater risk of OSA. It was demonstrated that tobacco smoke contains a thousand compounds potentially harmful to human health such as heavy metals, nicotine and volatile organic compounds that increase oxidative stress and systemic inflammation, which play roles in the occurrence of cardiovascular, metabolic and cognitive disorders (24,25).

In another hand race and social environmental factors influence the CPAP adherence. Scharf et al. suggested that in African-American, CPAP usage rates are lower than in Caucasian, probably because of socioeconomic status. From a clinical perspective,

a plan which takes into consideration the individuals characteristics should be developed for diverse patients groups (26).

Another factors that influence the compliance to CPAP therapy are patients comorbidities, moreover, pulmonary diseases.

Chronic obstructive pulmonary disease (COPD) is a comorbidity often related with OSA, and their association is known as “overlap syndrome” (27). This syndrome has a prevalence of 1.0 to 3.6% in the general population, 366% in COPD patients and 8-56% in OSA patients (28). In 45% of the cases who have poor sleep quality and hypoventilation episodes during sleep, a severe form of OSA has been diagnosed. Higher rates of mortality were found in patients with overlap syndrome compared to OSA ones, confirming that a right and complex management of both pathologies is required (29, 30). Asthma is frequently associated OSA, both having many nocturnal and diurnal symptoms in common like poor sleep quality, excessive daytime sleepiness and poor quality of life. The prevalence of OSA is about 49% in patients with poor asthma control (31).

Treatment titration procedures

With the increasing prevalence of OSA, there are more demands for sleep diagnosis and titration services. There are two ways to deliver continuous positive airway pressure: a standard mode airway pressure (CPAP) and an auto titrating mode (APAP). Ayas et al compared APAP and CPAP devices and concluded that age was associated with adherence differences, younger participants favoring APAP to CPAP (32). However, Hukins et al reported that there were differences between the two titration modes in side effects, with fewer adverse reactions reported by the ones using APAP (33). Massie et al conducted a study including subjects which required CPAP pressures >10 cmH₂O randomly treated with CPAP or APAP for 6 weeks and observed that even if there were no differences between the groups concerning the number of nights CPAP was used, the duration of use was higher in APAP group (34). So, the clinicians must take into account the initiation of APAP therapy mode for certain subjects, including younger persons, those with persistent side effects on CPAP or those needing higher CPAP pressures (19).

In addition, in patients with low tolerance with standard CPAP, APAP mode may become an add-on option to enhance overall compliance (19).

Technological device factors and side effects

Two third of CPAP users complains about side effects including claustrophobia, pressure intolerance, interface leak, nasal dryness, dermatitis, rhinitis, epistaxis, congestion, barotrauma, aerophagia and bloating. There are other patophysiological conditions that can interact with CPAP adherence including allergic or vasomotor rhinitis for which patients require counselling allergen avoidance advice, appropriate education and treatment with intranasal steroids or antihistamines. The development of these adverse events contributed to the innovation of comfort-related technological advances.

When speaking about side effects, the main concern refers to mask comfort but there are few studies that examined the effects of leaks, mask selections, mask changes or fit on CPAP compliance (35). Still the studies approaching this subject haven't found a significant influence of the mask interface on CPAP adherence. In order to combat the nasal/pharyngeal dryness it has been developed a system of heated humidification, important in OSA treatment, moreover because CPAP is capable to produce airway inflammation, to modify mucus transport and ciliary motility responsible for discomfort. But heated humidification is not recommended for the first CPAP initiation. By contrast, Sommer et al. observed a decreased mucus transport and an increased ciliary beat frequency in patients using CPAP with heated humidification compared to standard CPAP (36). In addition, Nilius et al. found that patients which used heated humidification had a better improvement in nasal symptoms but this did not significantly improve compliance except for the patients with nasal pharyngeal complains (37). Massie et al. found that CPAP adherence in OSA subjects is improved by adding heated humidification, so patients experienced greater satisfaction with an refreshed attitude in the morning based on the fact that they used CPAP more in the night (38). Rakotonanahary et al. developed a system of markers that can appreciate the need of humidification: presence of chronic mucosa disease, age more than 60 years, drying medications or uvulopalatopharyngoplasty (39).

The initial acceptance of CPAP is influenced by the presence of claustrophobia, so as Weaver et al. identified, about half of newly-diagnosed patients stated that they do not want to use CPAP if they feel claustrophobic (40). In contrast, even if at the

beginning of treatment the claustrophobia influence the CPAP compliance, the persistent use of the machine may improve the claustrophobia feeling and not necessarily lead to non-adherence (19).

d. Psychosocial and social factors

There is a multifactorial nature of CPAP adherence influenced by psychological and social factors which include self efficacy, risk perception of disease, coping mechanisms used in challenging moments, knowledge, treatment outcome expectancies and common treatment related expectancies. Many subjects does not associate their OSA diagnosis with depression, car accident, sexual performance, impaired concentration or memory and falling asleep while driving. In contrast, 66% of patients treated with CPAP realized that after treatment they were more alert and 53% had an improvement in sexual performance and desire. Through the system of self-efficacy measure in sleep apnea (SEMSA), Sawyer et al. found that outcome expectancies and self efficacy were important factors in CPAP adherence, so cognitive perceptions are important contributors to daily perceived responses of effective sleepiness (19).

Another factor that influences the OSA patients CPAP tolerance is the bad partner's opinion. McArdle et al. evaluated the bad partner's quality of life and sleep quality in OSA patients treated with CPAP and after one month of therapy. In subjects which received active CPAP, the bad partner's reported less sleep disturbances and a better sleep quality (41). These effects influence the subject decision to follow CPAP therapy (19).

What Interventions Promote CPAP Adherence or Compliance?

OSA treatment must include a multidisciplinary approach targeting symptoms control in order to provide a greater quality of life. Beside CPAP therapy, alternative options include weight control, oral appliance, mandibular advancement devices, upper airway stimulation, oropharyngeal exercises, and a number of upper airway surgical approaches (8).

In patients with severe OSA it is important to recognize and implement the strategies capable of improve the adherence to CPAP in order to accomplish a good health and an adequate functional outcomes. These interventions must be examined in terms of cost benefit ratio, clinical utility, resource utilization and patient acceptance (19).

Lifestyle intervention

Obesity is the main risk factor for OSA, and over 60% of patients with OSA are affected. It is a well-known fact that obesity is the most significant risk factor, with other factors such as smoking, alcohol abuse, male gender, the use of sedative medication, age, increasing the risk of developing OSA (42,43). Recently, it has been found a correlation between the body mass index (BMI) and AHI, so weight loss has become an important strategy in the management of OSA and all patients should be encouraged to control their weight. In addition, it is a well known fact that physical activity (PA) is a key determinant for good health. A PA plan is structured, scheduled, repetitive and purposive in order to improve one or more objectives [44]. Moreover, several studies have demonstrated that low levels of PA are associated with higher incidence of OSA, obesity, and metabolic syndrome (45, 46,47). Due to fatigue or excessive daytime sleepiness, many patients with OSA are unable to do physical exercises (45,48). The physical activity has multiple beneficial effects on OSA, such as improving the fatigue, decreasing the severity of central sleep apnea in patients with chronic heart failure, reducing the occurrence of cardiovascular diseases and improving the severity of OSA (49). The current guidelines recommends training programs as a treatment option for patients with OSA, taking into account that that regular exercises reduces the prevalence of OSA (50,51). Several recent studies have investigated the role of oropharyngeal myotherapy (OMT) on OSA, considering the role of the dilator muscles of the upper airway. Oropharyngeal exercises are a treatment modality capable of increasing sensitivity, coordination, strenght of orofacial structures, proprioception and mobility. At the same time, OMT favors a good performance of respiration, speech, deglutition and mastication (8). In addition, lifestyle interventions refers to measures that encourage the patients to quit smoking, reduce the alcohol intake and minimize the use of sedative medications (52).

Educational strategies

Educational strategies are recognized as a standard of care in the management of OSA patients and have become an important factor for the acceptance of CPAP treatment. In the healthcare plan, the clinician must include reinforced education interventions with increased frequency that must provide expanded explanations. Golay et al. developed a study including OSA patients which received a variety of

educational strategies (demonstrations, discussions, videos) and obtained a raise in the CPAP adherence at 3 months (53). Another study focused on behavioral therapy providing two 45 min one-on-one therapy sessions and concluded that at 12 weeks the adherence was substantially increased (54). It was developed a motivational enhancement therapy (MET) consisting in interventional viewing in order to highlight the patient's own motivating statements around therapy. It was proved that MET along education was efficient in patients with moderate adherence, but with no effect in patients with poor adherence (55). Another measure introduced to enhance the CPAP compliance is testing cognitive-behavioral therapy (CBT), which included a video of recent CPAP users and which describes their experiences, providing specific information's about goal development, symptoms, treatment relevance and expectations, cognitive testing performance and changes in symptoms with CPAP. This intervention was developed by Richards et al. and it was associated with higher scores for outcome expectancy and self-efficacy due to increased time spent discussing OSA as well as hearing about real experiences of CPAP users via the video. Its role it's to correct distorted beliefs, promote treatment initiation and positive perspective toward CPAP and enhance CPAP knowledge (56,57).

Since social support is associated with CPAP greater compliance, an alternative approach to CBT/MET requires group therapy with experienced CPAP users offering support and encouragement (58). In contrast Parthasarathy et al. observed that peer support had no influence on CPAP tolerance even if is more efficient than individual education, however one pilot trial offering peer support one on one demonstrated a significantly higher adherence during the first week of CPAP therapy which persisted over the first 90 days of therapy (59).

Behavioral therapy customized to increased CPAP compliance is low risk intervention that can be incremented in the standardized management. Still approaches such as CBT/MET require highly trained stuff, which has limited their applicability in clinical evaluation (12).

Technological strategies

The ability to monitor CPAP compliance and other important therapy parameters such as pressure profiles must click and estimated residual disease provide potential to use remote monitoring or telemedicine in order to implement a web-based

adherence intervention. The role of these strategies include: targeted troubleshooting, personalized feedback for patients through web-or-app based education via a coaching website or smartphone app. The telephone-linked communication device (TLC) additional to usual care functioned as a monitor of CPAP use, educated and counselor with automated responses offered subjects included weekly calls, had a significant effect on CPAP compliance. Another intervention called tele-health provided a higher CPAP use at 12 weeks in OSA patients compared to placebo (60). In contrast, telemonitoring had no effect on adherence, neither the computer-based “health-buddy” introduced by Taylor et al. which included internet information, feedback and support with no statistical differences between intervention and control group (61). In contrast Kuna et al. obtained a raise of CPAP compliance by giving access to web-based feedback (62). By providing automated feedback, Hwang et al. concluded that it is a helpful instrument to obtain and sustain a long term beneficial effect on adherence (63). In 2018, Pepin et al. developed a multimodal approach including data from connected physical activity and sleep trackers, oximetry, home BP monitors in addition to CPAP telemonitoring data. It was observed that patients improved their daytime excessive sleepiness, physical activity, quality of life and CPAP compliance (64).

In the last years, manufacturers of CPAP machines had developed a theory driven coaching and support services including dashboard summarizing therapy data, educational materials, goal focused emails or text messages and troubleshooting materials, which had an impact on CPAP adherence in patients who used it (12).

So, the telemedicine is a method for rapid clinical implementation and its advantages include the ability to scale to large patient populations and to decrease the burden on clinical systems by reducing the need for office clinical visits.

Pharmacological strategies

In OSA patients using CPAP therapy which associate insomnia or anxiety, as Haniffa et al. recommends, the clinicians should introduce adjuvant hypnotic therapy additional to education, motivational interviewing and cognitive behaviour, to obtain a greater adherence (65).

Lettieri et al. examined the effects of a short time administration of Eszopiclone on 160 adults using CPAP therapy and observed an increase CPAP use, without significant adverse effects (66).

In addition, in order to maintain an adequate adherence to CPAP therapy is important to control the adverse effects. In patients with nasal obstruction, the standard first line treatment is medical therapy which include both steroids and antihistamines intranasal and systemic, alone or in combination. Siccoli et al. observed in subjects with allergic rhinitis which was treated with topical nasal steroids significant improvements in daytime sleepiness and sleep quality (67). There are evidence that suggests an improvement in sleep quality and a reduction of AHI in patients using nasal steroids (68,69). In contrast, intranasal decongestants are not so effective, with modest improvement in AHI scores (70). In patients with persistent nasal obstruction, there are two nasal dilators available, consisting in nasal valves which showed improvement in OSA with a decrease of AHI. So, the patients who have benefits of these systems may become candidates for definitive nasal valve repair (5).

Still, there are other otolaryngological factors that can contribute to failure of CPAP in relation to the nasal cavity and paranasal sinuses that can be corrected with surgical intervention.

Application modifications and patients interventions

In the last years, many non surgical and surgical options were developed for subjects who do not tolerate CPAP. Taking into account that higher CPAP pressures are associated with discomfort and side effects, the new CPAP technologies, allowed clinicians to deliver to patient's airway lower pressures, observation that need to be studied in extensive randomized trials. The auto titrating devices had demonstrated better tolerability but in clinical practice, many parameters have been suggested to predict CPAP pressure requirements: mean respiratory disturbance index, body mass index, gender, oxygen saturation, depression and mask leak (71, 72). The challenge is to establish the optimum CPAP pressures moreover because higher pressures are associated with CPAP induced rhinitis due to inflammatory changes in the nasal mucosa. Other pathological processes include sinusitis and nasal polyposis that can be missed during routine respiratory review but can be effectively treated medically or surgically (73,74).

Moreover, OSA patients following CPAP therapy need lifestyle interventions including a reduce alcohol intake, weight loss (bariatric surgery if indicated) and sleep positional therapy (5). The last

one can be highly efficient when used with other devices such a chin strap (69). However, these interventions have no significant long term effect on cardiovascular outcomes (5).

Another additional device useful in selective patients is oral appliance which involves the application of dental splits to prevent upper airway obstruction during sleep. The therapy efficacy is determined by the level of advancement but this device is indicated in patients with mild OSA (75). Mandibular advancement splints (MAS) action by protruding the hyoid bone anteriorly along with the mandible in order to increase the retroglossal distance, but this device can cause discomfort. However, it is contraindicated in patients with poor dentition or uncontrolled epilepsy. Their clinical use is indicated in subjects with retrognathism or bulky tongue, in combination with CPAP, even if there is no greater effect on cardiovascular outcome (76, 77).

Conclusions

In conclusion, obstructive sleep apnea is a high prevalent disorder responsible for a significant health and socio-economic burden. In cases of moderate or severe OSA, CPAP therapy is recognized as a gold standard treatment. Its role is to maintain the airway open and to prevent the nocturnal collapse of the airway. CPAP is considered to improve the symptomatology, the specific quality of life and the cardiovascular outcome. In order to obtain these effects, the patients should achieve an adequate compliance despite the side effects, such as dermatitis, epistaxis, rhinitis, nasal congestion, mask leak, barotrauma, aerophagia and claustrophobia.

The clinicians should implement measures taking into account the disease and patients' characteristics, the titration procedures, the evolution of the technological device and the psychosocial and social factors. The interventions that can promote CPAP adherence are based on lifestyle changes, physical training, educational strategies, social support, technological and pharmacological strategies and the usage of devices that can minimize the CPAP side effects.

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Pulmonary rehabilitation in severe post-tuberculosis sequelae - case presentation

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Abstract

Pulmonary tuberculosis (TB) still represents a challenge for the healthcare systems, in the active but also in the chronic phase, when TB sequelae may appear. Anatomical changes and destruction of lung parenchyma lead to loss of pulmonary volumes. The patients with post TB sequelae are expressing dyspnea, chronic cough, muscle weakness and reduced daily activity. We present the case of a 58 years old patient, with post TB sequelae (2 episodes of relapses), presenting dyspnea, chronic fatigue and bronchiectatic syndrome. He was included in a 8 weeks multidisciplinary pulmonary rehabilitation program, which comprised exercise training, airway clearance techniques, education. The results of PR program were positives: decrease of dyspnea (one point in mMRC scale), improvement of exercise tolerance (58 m gain at 6MWT), improvement in life quality (SGRQ decrease with 5.2 points). In conclusion, pulmonary rehabilitation may be a useful therapy in the management of post tuberculosis sequelae.

Key words: *tuberculosis, sequelae, rehabilitation, exercise,*

Introduction

Tuberculosis (TB) represents still a major health problem. Although the disease impact is major in the active phase, the TB sequelae also represent an important burden with long term consequences. The interventions that can be made in this chronic stage of disease sequelae are pulmonary rehabilitation, oxygenotherapy, nutrition and psychological counselling (1). Pulmonary rehabilitation (PR) is an evidence-based treatment conducted by a multidisciplinary team, addressed to the patients with chronic respiratory disease who has symptoms and a reduction in his daily activities (2-4). The main purpose of rehabilitation is to improve patient life and autonomy (4).

Case presentation

We present the case of a 55 years old man, non-smoker, hospitalized in our clinic for dyspnea, productive cough, and asthenia. The patients' medical history included two episodes of extensive pulmonary tuberculosis 8, respectively 1 year before, treated effectively for 6, respectively 9 months. After the last episode, he rested with chronic cough, bronchoreea, and decreased effort tolerance. At the presentation in the pneumology department, a new tuberculosis relapse was suspected and a sputum smear microscopy was performed, with no evidence of acid fast bacilli.

Clinical examination reveals cachexia (BMI index 17.2 kg.m²), impaired general status, clubbing, muscle deconditioning. At the level of the respiratory system, the vesicular murmur was present bilaterally, without bronchial rales, respiratory rate 18 / min, the SaO₂ was 95% at rest. Spirometry performed showed mixed syndrome: FEV₁ =1.64 L (54.4% predicted), FVC=2.12 L (46.4% predicted). The exercise tolerance was assessed by the 6 minutes walking test (6MWT). The 6 minutes walking distance was 423 m (58% of predicted value), with increase in dyspnea on BORG scale from 2 to 5 and significant desaturation from SaO₂= 95 to 91%.

Due to importance of the symptoms (dyspnea, chronic cough), severe muscle weakness and decrease effort tolerance, the participation to a pulmonary rehabilitation program was proposed. The parameters followed before and after rehabilitation program were:

- **dyspnea:** measured with mMRC (modified Medical Research Council) dyspnea scale who has a value of 3 from 4 (score range from 0 to 4); higher score mean worse symptoms

- **functional lung tests:** forced vital capacity (FVC), first expiratory flow in first second (FEV₁)

- **exercise tolerance:** measured with 6 minutes walking test 6MWT (performed twice according to ATS criteria, the highest distance traveled was choosen) and cardiopulmonary exercise test CPET (maximum oxygen uptake VO₂ max was 20.05 ml/min and maximal power 85 watts)

- **quality of life** was assesed with SGRQ (St. George Respiratory Questionnaire, score range from 0 to 100, with high score showing impaired quality of life; in this case, the total score was 51.58 points (sympmtoms score 43.9, activity score 66.31, impact score 45.25).

Pulmonary rehabilitation (PR) program was multidisciplinary, outpatient, during 8 weeks (three sessions per week) and consisted in exercise training, chest physiotherapy, therapeutic education. Before entering in the PR program, the patient signed an informed consent approved by the ethical committee.

The lower limb exercise training was aerobic, endurance training, performed on a velo, 30 minutes per session. For the intensity of training we used the maximal power obtained during the cardiopulmonary exercise test (CPET). The velo charge in watts was set up in order to reach progressively the 60% of the VO₂ max (20.5 ml/min). During every session of 30 minutes cycle training there was a 5 minutes warm-up and recovery period. The upper limb training was performed with weights, using 3 series of 10 exercise separated by a 5 minutes break. The weights have been increased progressively.

Given the presence of post TB bronchiectatic syndrome, a special concern was given to cough management and airway cleaning techniques. He was learned how to obtained an effective cough, breathing exercise, postural drainage. These exercises were firstly made under the supervision of a healthcare professional, and afterwards he continued at home daily.

He also performed daily positive expiratory pressure with a Treshold device (figure 1), that contain a unidirectional valve that opposes a resistance when the patient expire. These exercises were performed daily, 15 minutes twice daily and were continued after the PR program finished.



Fig. 1. Treshold PEP (Positive Expiratory Pressure)

After the PR program, dyspnea score decreased with one point (mMRC scale), and SGRQ score with 5.2 points. Regarding the exercise tolerance, there was a significant improvement in 6MWT distance with 58 m, and VO₂ max with 1.38 ml/min (table 1). A diminution of the cough frequency with sputum discolouration was noticed.

Parameters	Before rehabilitation	After rehabilitation
Dyspnea mMRC (points)	3	2
FEV1	1.64 L (45.4% predicted)	1.73 L (49.2% predicted)
FVC	2.12 L (46.4% predicted)	2.19 L (47.2% predicted)
6MWT (m)	423	481
Pmax (Watts)	95	105
VO ₂ (ml/min)	20.05	21.43
SGRQ score (points)	51.58	46.38

Table 1. Parameters evaluation before and after rehabilitation program

Discussion

Pulmonary tuberculosis, even with successful chemotherapy, can lead to important loss of pulmonary function. Although the bacteriological sterilisation of the lesions is achieved, the sequelare scars may amputate lung parenchyma, resulting in loss of pulmonary volumes. The structural alterations are varied, from fibrotic scars, bronchiectasis, bronchial stenosis, broncholitiasis. The incidence of post TB functional impairment varies in the literature, from 33 to 94% (4-7). In a Portuguese study that measured pulmonary function in 214 patients treated for tuberculosis, almost half of them (47.7%) have impaired lung function, the most common finding being the obstructive syndrome (34.6%) (8).

Lee studied the chronic airflow obstruction in post TB destroyed lung and compared with COPD patients, the results showing that pulmonary function in post TB destroyed lung patients (both FVC and post bronchodilators FEV1 values) were lower than in COPD control group (9).

The patients with relapses of tuberculosis are at a very high risk to develop functional impairment, pulmonary volumes decreasing after each new episode of tuberculosis, as showed in study of Hnizdo. In a group study of 2599 black South African gold miners with one, two or three episode of TB in medical history, a decrease of FEV1 was found with 153 ml, 326 ml, and 410 ml, respectively after one, two or three episodes of tuberculosis (10). Also, in post TB syndrome, it seemed to be in an inverse relationship between the magnitude of the disease on chest radiography and the forced expiratory volume in one second (FEV1)(11,12).

These functional disabilities are accompanied by decrease exercise tolerance and loss of autonomy, having a negative effect on usually daily activities. The breathlessness, the fatigue, the irreversible aspect of the disease, social isolation may also lead to a depressive syndrome.

Pulmonary rehabilitation (PR) is an individualized and comprehensive intervention, performed by a multidisciplinary team, addressed to patients with chronic respiratory disease, such as post TB sequelae. The indication of PR programs are patients with symptoms, impaired exercise tolerance and low quality of life. In post TB sequelae, there are two major directions of pulmonary rehabilitation. One is address to dyspnea and subsequently functional disability and the other one to the bronchiectatic syndrome.

Unlike COPD, there are few studies available about pulmonary rehabilitation in post tuberculosis syndrome. For the patients with impaired effort tolerance and reduction of daily living activities, exercise training can be proposed. Although the muscular training is shown to have positive effects on exercise performance (13,14), there are not clear recommendations (as in COPD) for the intensity of training and the optimal threshold.

A study from Colombia folowed the effects of a 8 weeks PR program on aerobic capacity of patiens with post TB sequelae. The program includes exercise aerobic training and education. The lower limb training was performed on a treadmill, with progresively load increasing from 60 to 85% of maximum oxygen consumption (VO_{2peak}). The

positives changes were statistically significant for exercise tolarance (the VO_{2peak} increased by 1.7 mL/kg/min and 6MWD increased by 63.6 m), as for quality of life (SF-36 physical domain score increased by 6.98 points, whereas the SGRQ score increased by 13 points)(14).

Another study conducted in Japan compared the results of a nine week outpatient PR program in 32 post tuberculosis patients and 32 COPD patients. The positive effects were similar in the 2 groups, in terms of exercise tolerance (6MWT distance), dyspnea (MRC scale), daily activites scores (15).

Regarding our patient, the pulmonary rehabilitation program design was similar with the one used for the other COPD patients participating in the PR program. Before the rehabilitation, cardiopulmonary exercise test was used to find the maximal workload, who was 105 watts. The training was start at 60% of this load and was increase progressively at every session in order to reach 80% of the load. The benefits were obtained in symptoms, exercise tolerance (6 MWD increase with 58 m), but also in QOL (decrease of SGRQ score with 5.2 points).

As in the other type of bronchiectasis, in post TB bronchiectasis, one of the main concerns is the ineffective cough and sputum retention. The main scope is to increase the expectoration, through different techniques: controlled cough, postural and autogenic drainage, vibrations, percussions, positive expiratory pression, aso (16).

In our patient's case, respiratory physiotherapy was performed, first in the PR center and after the patient learned how to set up, he continued at home daily. Airway cleaning techniques were used, together with special devices as Threshold and lead to a discoloration of sputum and reduction in the daily amount of sputum.

In one year follow up after the PR program, the patient clinical status rested good and he suffer no other infectious exacerbation.

Conclusion

In our patient with sequelae from multiple relapses from tuberculosis that lead to functional and social disability, the pulmonary rehabilitation was safe and successful. These cases may represent good candidates for PR programs and exercise together with airway clearance techniques must be a part of their long term management.

Conflict of interest

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 article

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The effects of regular physical activities on subjective well-being levels in women of menopause period

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Abstract

This study was conducted to examine the effects of regular physical activities on subjective well-being levels of women in menopausal period. The participants of the study is composed of 36 women with menopause in total, an exercise group (EG) including 21 women (average 50,04 years of age) and a control group (CG) including 15 women (average 51,93 years of age). Data from the independent variables of the study were collected via the Personal Information Form which was developed by the researchers. The Subjective Well-Being Scale (SWS) was used to identify the positive psychological states of the participants in pre and post tests for 8 weeks. The ultimate criteria of the study are to integrate the subjects who had not exercised for at least six months, and agreed to participate in this controlled trial voluntarily. During the 8 weeks, the EG practised two mat Pilates classes three times per week lasting 1 h each, supervised by the same qualified Pilates instructor. Paired Sample t test was used to compare the pre and post test of the normally distributed parameters. The data obtained were evaluated at $p < 0.05$ significance level. The results of our study demonstrated that, compared to a control group, the Pilates group exhibited significant improvements in Subjective well-being in 8-week exercise sessions. There was no significant improvement in control group after 8 weeks. It was concluded that the aerobic pilates exercises training had positive effects on Subjective Well-Being. Therefore, regular aerobic exercise training as an effective strategy in improving positive psychology among women with menopause is highly recommended.

Key words: *menopause, subjective well-being, physical activity,*

Introduction

Women's life consists of stages such as childhood, adolescence, maturity, menopause and old age. Menopause is one of the most important stages of women's life. As in other life periods, biological, psychological and social changes are experienced in menopause.

Menopause refers to cessation of ovarian follicular activity and is manifested by the cessation of menstrual flow lasting at least 12 months (1). Menopause represents one of the most important physiological periods in a woman's life, defined by a series of involutive processes (the cessation of reproductive and menstrual functions) and the transition from the reproductive phase to the non-reproductive phase (2). The interactions between psychological and biological factors determine the body's reactions to hormonal changes occurring in menopause (3). In menopausal period, different problems may arise from estrogen deficiency in women, vasomotor symptoms to mental symptoms and from sexual function changes to osteoporosis,

muscle-joint pain, headache, hot flashes, decreased sexual desire (4). Also some of the psychological symptoms include: stress, anxiety, irritability, depressive tendencies and difficulty on concentration. The age at which menopause occurs is an average of 49, but individual variations may occur and can be experienced at an older age (5).

Attitudes to ageing exert a powerful influence on health and well-being in the second half of life. Longitudinal data have demonstrated that those with a positive attitude to their experience of ageing lead a healthier lifestyle and are less prone to morbidity and mortality relative to those with a negative attitude to ageing (6,7).

In recent years, it has been found that women resort to alternative ways of coping with menopausal problems. Most interventions for menopause women have focused on: educational intervention, physical activity/exercise, improving a healthy diet, stress management, healthy behaviors, preventing certain diseases (8).

Physical activity is an international term and is an expression used to describe body movements using energy. It is called all body movements that are done with skeletal muscles and result in energy expenditure (9). Physical activity is the activity performed by the energy expenditure that occurs as a result of the movement of the body through skeletal muscles, increasing the heart and respiratory rate, can be performed at different intensities and result in fatigue (10). The advantages of regular physical activity include reduction in risk of cardiovascular events, reduction in obesity, diminished risk of hypertension and diabetes mellitus, improvement in blood lipid profile, reduction in risk of cancer and many others (11). Physical activity causes many physiological changes in the body, as well as affecting the psychological structure of people, which is a case studied in the psychology literature in the last decade and demonstrated that exercise plays an important role in the development of positive mental health. This finding is based on an increasing number of experimental studies that describe the positive effects of exercise (12).

Positive mental health has gained importance in the field of positive psychology since the early 2000s, and has focused on working on concepts such as happiness, well-being, satisfaction, life satisfaction, optimism, psychological resilience, hope and trust (13,14).

Subjective well-being is a good indicator that can be used to demonstrate the psychological quality of life of an individual. Subjective Well-Being is defined as people's overall evaluations of their life and their emotional experiences. Subjective Well-Being thus includes broad appraisals, such as life and health satisfaction judgments and specific feelings that reflect how people are reacting to the events and circumstances in their lives (15).

Many studies have shown a positive association between physical activity and Quality of life among middle-aged women (16,17). In a study with women with menopausal symptoms, moderate levels of physical activity were associated with reducing not only physical but also psychosocial menopausal symptoms and suggesting that physical activity may improve some of the symptoms of menopause, thereby increasing the quality of life in menopausal women (18,19).

Physical activity has been investigated as a potential remedy for menopausal symptoms with conflicting results (20). but there is a lack of research on

menopausal symptoms as potential reasons for being physically active or inactive.

Due to this deficiency in the literature, the effect of regular physical activity on subjective well-being of women in menopausal women has been aimed to be examined and pilates exercises have been preferred at this point. The Pilates exercise system is a composite of movement styles and philosophy of gymnastics, martial arts, yoga, and dance (21). and various positive physical and psychological effects of regular pilates training were reported in healthy individuals, as well. And in the studies concerning psychological functioning, significant improvements in sleep and life-quality were found among university students, middle aged people, and the elderly population after pilates training (22).

Although studies have explored the potential benefits of regular physical activity and pilates exercise, not much association has been investigated between a pilates-based exercise programme and positive psychology parameters. The aim of this study, therefore, is to investigate whether 8 weeks pilates-based programme improve subjective well-being level of women with menopause. In accordance with this purpose, responds to sub-problem below is investigated:

1- Do regular exercises (8 weeks pilates based program) increase the subjective well-being level of women with menopause?

Materials and methods

In order to determine the effect of regular physical activity (pilates exercises) on the subjective well-being levels of women with menopause, "Pretest-Posttest Control Group Semi-Experimental Pattern" was used. Semi-experimental patterns are a model with high validity in researches in areas where it is not possible to control all variables (23). In order to measure the effect of regular physical activity carried out with the Pilates exercise program on the subjective well-being levels of women with menopause, experimental and control groups were created randomly in line with women's pretest scores. Subjective Well-Being Scale was applied to each group simultaneously. An 8-week pilates exercise program was carried out with the experimental group, and no intervention was made to the control group. As a result of the experimental application, Subjective Well-Being Scale posttests were applied to both groups simultaneously. The subjective well-being levels of menopausal women who participated in the study were compared with the posttest applied.

Participants

Thirty-six women with menopause constituted the participant group of this study. All of them live in Erzincan, Turkey. The participants were randomized, with a draw, into an exercise group, (EG) 21 women; average age 50,04; and a control group, (CG) 15 women, average age 51,93. The ultimate criteria of the study are to integrate the subjects who had not exercised for at least six months, and agreed to participate in this controlled trial voluntarily.

Instruments

The personal information form: Data on the independent variables of the study were collected with the Personal Information Form which was developed by the researcher. Questions consist of some information such as womens' age, perceived economic status, perceived parental attitude, satisfaction with physical appearance.

The subjective well-being scale (SWS): The SWS was developed by the researcher (24). The scale consists of 46 items. By assessing individuals' cognitive appraisals of their lives and the frequency and intensity with which they experience negative and positive feelings, the scale intends to measure their degree of subjective well-being. The SWS

assigned points 1 to 5, whereas negative items are assigned points 5 to 1. The lowest possible score on the scale is 46 and the highest is 230. Higher scores indicate higher degree of subjective well-being. The construct validity of SWS was examined by principle component analysis. Factor analysis revealed a KMO coefficient of .86. The shared variance of factors on each variable ranged from .51 to .75. The eigen value of the SWS revealed 12 factors with values greater than 1. The first factor accounted for 24.52 % of the total variance. The factors of the scale accounted for a total variance of 63.83 %. The factor weights of the items on the first factor ranged from .30 to .66. For concurrent validity, correlations between scores on SWS and Beck Depression Inventory were calculated (25). As to be expected, there is a significant negative relationship between scores on the two scales ($r=-.70$). Internal reliability for the SWS was a Cronbach-alfa coefficient of .93. In order to determine test re-test reliability, the scale was administered to 39 persons. The time interval between two administrations was two weeks. Test re-test reliability yielded a correlation coefficient of $r = .86$

Procedures

During the 8 weeks, the EG maintained three times per week frequency of two mat Pilates classes lasting 1 h each, supervised by the same qualified Pilates instructor. The exercises given during the first two weeks of the intervention were designed and standardized according to the Classical Pilates Method. For the next 6-weeks of the intervention, the exercise protocol was amended by adding new intermediate-level exercises. This was possible because the participants in the study demonstrated quick learning and assimilation of the PM during the first two weeks of the intervention. Throughout the entire period of Pilates Method training, the participants reported no discomfort. We used the following activities on the intervention: a series of pre-Pilates and Pilates for beginners, with the goal of completing the series of Pilates at the intermediate level.

Data analysis

The data obtained from the study were analyzed in SPSS (Statistical Package for Social Sciences) for Windows 21.0. Paired Sample t test was used to compare the pre-test and post-test of the normally distributed parameters. The data obtained were evaluated at $p < 0.05$ significance level.

Table 1. The pilas exercise program

Exercises	Equipments	Repetitions
The hundred	Mat	8
The shoulder bridge	Mat	8
Single leg circle	Mat	8
One leg stretch	Mat	8
Double leg stretch	Mat	8
Rolling like a ball	Mat	8
Leg pull down	Mat	8
Leg pull up	Mat	8
Pelvic curl	Mat	8
Side bend	Mat	8
Side kick front	Mat	8
Side kick back	Mat	8
The saw	Mat and with ball	8
Roll-up	Mat and with ball	8
Spine stretch and spine	Mat and with ball	8
Stretch forward	Mat and with ball	8
Push-up	Mat and with ball	8
Bent-knee bride	With ball	8
Single leg stretch	With ball	8

includes evaluative statements about major domains of life and about positive and negative emotionality. A 5-point Likert scale is used: "(5) fully agree;" "(4) mostly agree;" "(3) "agree;" "(2) somewhat agree;" and "(1) disagree." Each item has a score ranging from 1 to 5. There are 26 positive and 20 negative statements. In scoring, regular (positive) items are

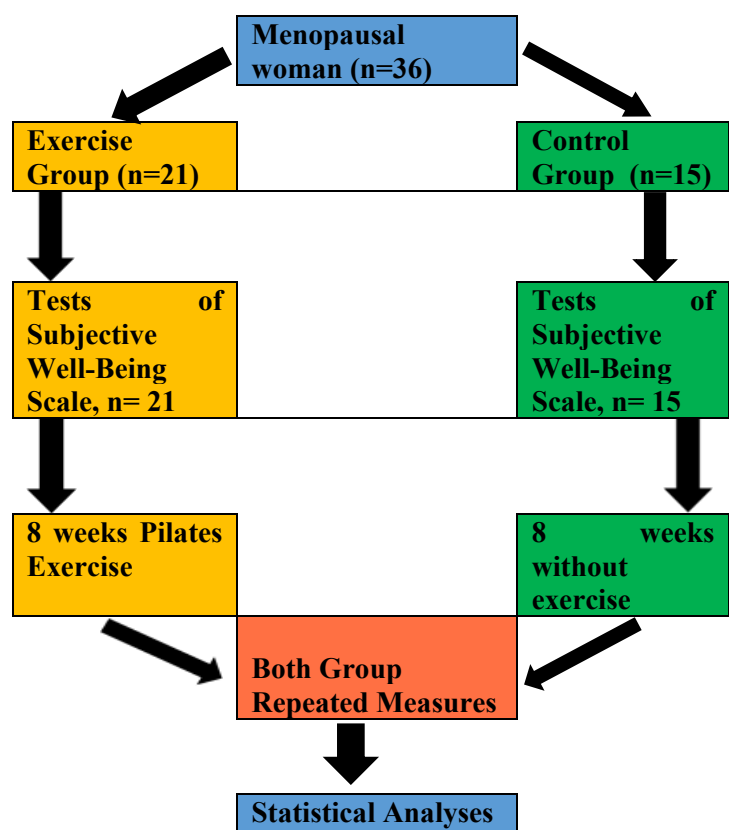


Fig. 1. Flow chart illustrating the design of the study

2.5. Ethics approval

This study was approved by the Ethics Committee of Erzincan Binali Yıldırım University of Scientific Research (Decision number: 2019.05.05-03). The researcher gave oral and written information and obtained written informed consent from all participants before the interviews. Participation was voluntary, and the participants had the right to withdraw at any time

3. Results

Results are reported in Table 2. As seen in the table, subjective well-being scores were significantly improved in the exercise group after 8-week pilates program, there was no significant improvement in control group as seen.

Table 2. Analytical data for subjective well-being pre-test / post-test score differences

Factor	Exercise Group (n=21)		Control Group (n=15)		t
	\bar{x}	s	\bar{x}	s	
Before Exercise (Pre-Test)	141,76	21,97	178,73	26,62	4,60
After 8 weeks exercise (Post-test)	172,33	20,43	175,40	24,97	-.344
Paired t-test / p	.000**		.590		

4. Discussion

This study was designed to assess the effects of 8-week aerobic pilates exercises training on Subjective Well-Being of menopausal women.

Results of our study demonstrated that the subjective well-being scores were higher after 8-week of pilates in the exercise group. There was no significant change in the control group after 8 weeks. The literature on physical activity provides a compelling argument in support of physical activity for improving subjective well-being in older adults and both the psychological health and cognition literatures suggest aerobic and non-aerobic exercise programs may benefit well-being in older adults (26). Elavsky and McAuley (2009) in a study conducted with women with menopause found that 4-month physical activity lead to a decrease in the average trait anxiety status of women (3). And another study emphasized the importance of an increase in physical activity for the psychological and physiological domains of menopausal women's life (27). Lim found that women with positive attitudes were able to manage menopause through regular exercise, demonstrating comparable results with their study (28).

There is strong evidence of a positive influence of physical activity on the proposed antecedents of quality of life and well-being, including self-related function, mood or psychological states (i.e., depression, anxiety, self-esteem, positive affect, self-efficacy) and cognitive function (e.g., executive function, working memory) in older adults (28-33). Ruuskanen and Ruoppila who reported that active older adults at the age of 60–75 had fewer depressive symptoms than their nonactive peers (34).

A number of previous studies have provided evidence that Pilates-based or Pilates-inspired exercise is able to improve a number of indicators of physical and psychological parameters in both the younger and more elderly populations. Boguszewski et al. found that physical activity and pilates exercises positively affect the physical and mental condition of women (35). Tolnai et al. (2016) stated that Pilates training only once a week, over a relatively short 10-week period, results in significant improved in physical and mood (22). Biddle (2000) has recently conducted a review of reviews on the literature (36). He concluded that there is clear experimental support for an effect of exercise on positive mood.

Both survey and experimental research therefore provide support to the well publicised statement that “*exercise makes you feel good*” (37-40).

Result of our study demonstrate that the menopausal women who took part in an 8-week of pilates exercising, three times a week, experienced increased Subjective well-being after the 8 exercise sessions.

Conclusions

Menopause is important to the psychology of women. Today’s women live a third of her life after menopause. Regular physical activity is one of the most important health behaviours associated with the prevention and management of chronic diseases in older adults and menopausal women.

We conclude that aerobic pilates exercises training has positive effects on Subjective Well-Being in menopausal women. Therefore, regular exercise training as an effective strategy in improving positive psychology among menopausal women is highly recommended.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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Clinical experience of using mineral water and vitafonotherapy in the complex treatment of patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease

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Abstract

Chronic viral hepatitis C (CHC) remains a significant medical and social problem worldwide and is a leader in the structure of etiological factors in the development of diffuse liver diseases (NAFLD). The presence of NAFLD in patients with chronic hepatitis C accelerates the progression rate of HCV infection and reduces the effectiveness and tolerability of antiviral therapy. The above circumstances initiated us to the search for new non-drug technologies for the treatment of this category of patients. The purpose of these work is evaluate the effectiveness of the integrated use of standard antiviral therapy, the drinking of low-mineralized silicon sodium bicarbonate mineral water (MW), and vibroacoustic therapy (VT) in patients with chronic hepatitis C with concomitant NAFLD. Research methods: anamnestic and clinical, general clinical, biochemical, serological (markers of viral hepatitis C, HCV RNA PCR (qualitative and quantitative determination, genotyping), quantitative determination of total endogenous α -interferon in the blood serum, ultrasonographic studies of the digestive system, statistical methods. Fifty patients with chronic hepatitis C (genotype 1b in the phase of replication, minimal and moderate activity) with concomitant NAFLD were examined. Patients were divided into two groups. Patients of the I (control) group (25 people) received the basic treatment complex, which included dietary nutrition (diet No. 5), standard antiviral therapy (AVT) (interferon alfa-2 b and ribavirin) for 12 months and internal intake of MW for the first month of treatment. Patients of group II (25 people), in addition to the basic complex of treatment, additionally received VT procedures, the course of which was six months. Evaluation of the effectiveness of treatment was carried out after 1, 3, 6, and 12 months from the start of treatment. The treatment in both groups was accompanied by the positive dynamics of most of the signs of the disease; however, a significant advantage of using VT was found. In patients of group II, the side effects of AVT - influenza-like and cytopenic syndromes - disappeared, interferonogenesis was stimulated, which made it possible to complete the AVT course in 92.00% of patients and obtain a virological response in 56.00% of patients. In other cases, reduce the virological load by no less than 2 log.

Key words: *chronic viral hepatitis C, non-alcoholic fatty liver disease, mineral water, vibroacoustic therapy,*

Introduction

One of the urgent problems of modern hepatology remains the treatment of patients with chronic viral hepatitis C (CHC), which is associated with an increase in the incidence and development of complications - cirrhosis of the liver and hepatocellular carcinoma (1, 2). Non-alcoholic fatty liver disease (NAFLD) is also one of the most common diffuse liver diseases in the world, which is associated with the global epidemic of obesity 3, 4, 5). Due to the significant prevalence of CHC and NAFLD, according to various experts, it is expected that these two nosological forms will be determined together in a substantial number of patients. The average frequency of identifying NAFLD associated with chronic hepatitis C is about 55%, depending on the genotype of the virus and metabolic syndrome (6). The interaction between chronic hepatitis C and hepatic steatosis is essential when conducting

antiviral therapy (AVT), predicting the rate of progression of the fibrotic process, and assessing the risk of hepatocellular carcinoma (7, 8).

Our scientific research began in 2011 when the “gold standard” for the treatment of patients with chronic hepatitis C was the use of linear or pegylated interferons in combination with ribavirin. The effectiveness of such treatment, that is, the achievement of a stable virologic response (SVR), ranged from 40 to 60%. Meanwhile, such therapy had a large number of contraindications and several significant drawbacks, namely, the development of severe side effects. The lack of effectiveness and high cost of treatment forced some patients to prematurely terminate the AVT or to not agree to such treatment at all (9, 10, 11). The above circumstances initiated us to the search and development of new non-drug technologies for

treating patients with chronic hepatitis C with concomitant NAFLD to increase the effectiveness of therapy and improve the quality of life of patients.

The purpose of the work is to evaluate the effectiveness of the integrated use of standard AVT, drinking low-mineralized silicon sodium bicarbonate MW, and VT in patients with chronic hepatitis C with concomitant NAFLD.

Materials and methods. We examined 50 patients with chronic hepatitis C (genotype 1b in the replication phase, with a minimum and medium degree of activity) with concomitant NAFLD, who were monitored in the clinic for rehabilitation treatment of patients with a gastroenterological profile of the State Institution "Ukrainian Research Institute of MR and KM of Ukraine".

The study used methods such as anamnestic and clinical, surveyed general clinical, biochemical blood parameters, serological markers of viral hepatitis C, HCV PCR RNA (qualitative and quantitative determination, genotyping), quantitative determination of total endogenous α -interferon in blood serum, ultrasonographic studies digestive organs, statistical methods.

Two groups of patients with chronic hepatitis C were formed with concomitant NAFLD. Patients of the 1st (control) group (25 people) were prescribed a basic treatment complex, which included dietary nutrition - diet No. 5, which corresponds to the Mediterranean diet (12), standard AVT (interferon alfa-2 b and ribavirin) for 12 months and internal administration mineral water (MW) during the first month of treatment. A prerequisite for our choice regarding the use of MW in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD was the availability of data on the atherogenic, insulinotropic, lipid-lowering, cardioprotective properties of MV with a sufficient content of hydrocarbons, sodium and trace elements (13, 14, 15). The data on the mechanism of the influence of trace elements on NAFLD are presented, and the basis for their therapeutic appointment in a patient with NAFLD is established (16, 17).

We used packaged silicon low-mineralized bicarbonate sodium water of well No. 242, the village of Shayan, Khust district of the Transcarpathian region (Ukraine). The total mineralization of MW was 1.86 g/l. The main anions in the chemical composition of MW were HCO_3^- (1.187 g/l), Cl^- (0.095 g/l), and among the cations, Na^+ and K^+ ions (0.447 g/l). Other cations and

anions - SO_4^{2-} (0.059 g/l), Ca^{2+} (0.064 g/l) and Mg^{2+} (0.008 g/l) had insignificant concentrations. In MW, there are biologically active components and compounds that are standardized in balneology according to the legislation of Ukraine (18), and add specific properties to waters. Such components are H_2SiO_3 (metasilicic acid) - 69.42 mg/l (silicones are considered MW with an H_2SiO_3 content of 50 mg/l and H_3BO_3 (Orthoboric acid) - 15.83 mg/l (boric ones are MW with an H_3BO_3 content from 35 mg/l). Patients of 2 groups (25 people), in addition to the basic complex of treatment, were additionally prescribed the procedures of vibroacoustic therapy (VT), the course of which was six months. The procedures were performed using the apparatus "Vitaфон IR". The primary mechanism of action of vibroacoustic therapy is the ability of micro-vibration waves to reduce the hydrodynamic resistance of blood vessels. Due to this, the osmotic movement of the fluid is enhanced, and the rheological properties of the blood are improved, which leads to an intraorganic increase in capillary blood flow and lymph flow in a radius of 7-10 cm from the center of the vibraphone.

Strengthening the capillary and lymph flow in the affected organs and tissues is considered a necessary and essential direction of therapy for chronic inflammatory diseases, including chronic hepatitis C. It aims to achieve resorption of inflammatory edema and tissue revascularization, as well as improving the delivery of drugs to the site of inflammation. Also, the effect of this effect on interferonogenesis is not excluded due to the increased yield of immunocompetent cells in interstitium and an increase in the frequency of their contacts between themselves and liver cells (19).

Evaluation of the effectiveness of treatment was performed after 1, 3, 6, and 12 months from the start of therapy. The age of patients ranged from 18 to 59 years, and the average age was (43.15 ± 11.32) years. The sex ratio was approximately the same: 27 women ($54.00 \pm 7.05\%$) and 23 men ($46.00 \pm 7.05\%$).

Statistical processing of the obtained data was carried out using the programs for biomedical research, Microsoft Excel 2010 and Statistica 6.0 (StatSoft, 2006). The average values are given in the form $(M \pm m)$, where M is the average value of the indicator, m is the standard error of the mean. Significant changes were considered to be those that were within the confidence limits according to Student's tables <0.05 .

Results and discussion.

Among the concomitant diseases of the digestive system, 50 patients examined more often had chronic pancreatitis - 36 (72.00 ± 6.35)% of cases, chronic non-calculous cholecystitis in 29 patients, chronic gastritis (atrophic and non-atrophic) was detected in 9 patients. When interviewing patients before treatment, most often (94.00 ± 3.36)% of cases) some complaints characterize the asthenic syndrome. Manifestations of dyspeptic syndrome disturbed (74.00 ± 6.20)% of the respondents. Pain abdominal syndrome occurred in (68.00 ± 6.59)% of cases. Analysis of the leading indicators of the hemogram showed that almost a third of patients have signs of anemia and leukocytopenia (respectively (26.00 ± 6.20)% and (28.00 ± 6.35)%), a reduced platelet count was observed in 25% of the examined. In (16.00 ± 5.18)% of patients, an increase in ESR level was determined. In biochemical studies, cytotoxic syndrome was most often observed: an increase in transaminases to 2-3 N (64.00 ± 6.79)% of patients; cholestasis syndrome was recorded less frequently - in (34.00 ± 6.69)% of patients. Thymol clouding was observed in (38.00 ± 6.86)% of patients. Signs of dyslipidemia were observed in all patients and were characterized by an increase in total cholesterol (TCH) on average to (6.85 ± 0.17) mmol / l, lipoproteins low-density (LDL) (4.09 ± 0.21) mmol / L, a decrease in the level of high-density lipoproteins (1.49 ± 0.13) mol / L. The atherogenic coefficient was (4.55 ± 0.22) units. The plasma glucose level was (6.49 ± 0.33) mmol / L; the insulin concentration was slightly elevated and averaged (18.59 ± 0.86) μ U / ml. In comparison the HOMA index was (5.27 ± 0.42) units, which indicated a pronounced insulin resistance (IR) in the examined patients.

Ultrasound examination of the abdominal organs revealed an increase in liver echogenicity and diffuse changes of varying severity in 86.00% of patients, which was accompanied by hepatomegaly in (68.00 ± 6.59)% of people. Sonographic signs of steatosis of the liver (distal attenuation of the echo signal, blurred vascular pattern, diffuse increase in the "brightness" of the hepatic parenchyma) were identified in all examined patients. Ultrasonographic signs of gallbladder pathology were noted in half (58.00 ± 6.98) % of patients, pancreas - in (52.00 ± 7.07)% of cases. Splenomegaly was detected in (12.00 ± 4.59) % of patients.

Assessment of interferon status demonstrated a significant decrease in the level of endogenous α -IFN in the absolute number of cases, with the average value being (1.57 ± 0.24) pg/ml, with reference values from 5 to 50 pg/ml. The treatment in both groups was accompanied by the positive dynamics of most of the signs of the disease; however, a detailed analysis revealed significant advantages in patients of group 2 with the use of VT. In patients of the 2nd group, after one month from the start of therapy, the manifestations of asthenic ($p < 0.05$) and pain ($p < 0.05$) syndromes significantly decreased, which was not observed in patients of the 1st group of the control, where only the trend was established ($p > 0.05$) to the dynamics of similar indicators. Positive dynamics of the syndrome of gastric and intestinal dyspepsia were observed in both groups. They were accompanied by normalization of an acid-forming function of the stomach in most patients ($p < 0.001$). Side effects typical of AVT, such as the flu-like syndrome, myalgia, joint pain in group I patients, were present in almost all patients and were leveled only after 3-5 injections of interferon. In patients of the 2nd group, flu-like syndrome was not observed in any case ($p < 0.05$), myalgia, and joint pain in the vast majority of patients (80.00 ± 8.16)% were weakly expressed. Signs of a cytopenic syndrome in the form of leuko- and thrombocytopenia during treatment were recorded in (40.00 ± 10.00)% and (36.00 ± 9.79)% of patients in the control group, respectively. The course use of vibroacoustic therapy in persons of group 2 prevented the development of cytopenia; a decrease in the number of leukocytes and platelets was observed only in (12.00 ± 6.63)% of patients. A decrease in the severity of the syndrome of cytotoxicity and cholestasis one month after the start of treatment in both groups did not occur. In patients of both groups during the entire course of treatment, there was a decrease in the concentration of total cholesterol and LDL ($p < 0.05$). At the same time the values of other indicators of the lipid profile did not change.

Analysis of the state of carbohydrate metabolism during all months of treatment showed a decrease in insulin resistance, including due to hyperinsulinemia. A tendency to a reduction of serum glucose ($p > 0.05$), a significant decrease in insulin concentration ($p < 0.05$), primarily due to hyperinsulinemia, which decreased by 1.6 times, was established. Due to this, a decrease in the HOMA-IR index ($p < 0.05$) was observed, although

reference values could not be achieved. During the first month of treatment in patients of groups 1 and 2, a significant ($p < 0.05$) improvement in the ultrasound picture of the biliary system was determined, namely, a tendency to restore the size of the gallbladder and a decrease in cystic sediment. Sonographic characteristics of liver tissue have not changed.

The study of the level of endogenous α -IFN showed the normalization of the process of interferonogenesis in both groups, and there were no significant differences between the groups. In group 1, the average level of endogenous interferon was 20.41 ± 2.87 pg/ml, and in group II - 25.00 ± 3.93 pg/ml ($p > 0.2$). A quick virological response (1 month after the start of therapy) occurred equally often - in 32.00% for patients of groups I and II.

After three months, the positive effects of the clinical course of the disease and the functional state of the digestive system persisted in patients of both observation groups. However, in the 1st control group only after three months, it was possible to achieve a statistically significant positive dynamics of asthenic and pain syndromes. Three months after the start of treatment, an increase in the cytopenic syndrome was determined in group 1 (leuko- and thrombocytopenia were recorded in $(64.00 \pm 9.79)\%$ of patients). In contrast, the use of BT in patients of group 2 made it possible to maintain the stability of hemogram indices, only in $(8.00 \pm 5.53)\%$ of cases did the decrease in the number of leukocytes ($p < 0.003$) occur. During the same treatment period, a statistically significant improvement in liver function tests was observed in both groups, although in group 1, it was slower for some indicators.

Improvement of ultrasonographic characteristics of the digestive system was more pronounced in group 2, where, along with the restoration of echogenicity and normalization of liver size, improved penetration of the echo signal into its deeper layers, the appearance of a homogeneous content in the gall bladder was observed in most patients $((80.00 \pm 8.16)\%)$. In all patients during the study, the pancreas had standard sizes, even and precise contours. Homogeneous structures were observed in most cases $((32.00 \pm 9.52)\%)$, although echogenicity of the gland in $((20.00 \pm 8.16)\%)$ of patients remained elevated.

An early virological response (after three months from the start of treatment) was recorded in 8.00% and 20.00% of cases in patients of groups 1 and 2, respectively, which indicates the use of

vibroacoustic therapy in standard antiviral treatment. A study of the state of interferonogenesis after three months of treatment showed further stimulation of endogenous α -IFN in patients of group 2. This effect is an adequate response to persistent viremia and proves the pathogenetic effect of the proposed method. In patients of group 1, a similar effect was not observed (table. 1). Control observation after six months of treatment indicated the preservation of the positive effects of the clinical course of the disease in the 2nd group of patients ($p < 0.001$). The stability of hemogram indicators, the functional state of the liver and its sonographic characteristics, and the restoration of the state of the system of endogenous α -IFN were observed. In contrast, patients of group 1 retained signs of a cytopenic syndrome, the biochemical response was slower, and there was no adequate response of the endogenous α -IFN system to persistent viremia. The achievement of a slow virological response after six months from the start of treatment was determined by 12.00% and 4.00% for groups 1 and 2 of patients, respectively. It should be noted that at the same time, there was a restoration of the functional state of the digestive system in patients with concomitant gastroduodenal and pancreatobiliary pathology, expressed more in patients of the 2nd group.

Further treatment in patients of group 1 during the 6th-12th months led to the development of some side complications characteristic of AVT, which forced to cancel therapy in $(20.00 \pm 7.94)\%$ of people. A third of patients in this group who continued to receive standard antiviral treatment experienced biochemical disturbances in the functional state of the liver (an increase in ALT and AsAT levels, an increase in the concentration of total bilirubin). The average level of α -IFN did not significantly differ from the previous indicator and amounted to (42.36 ± 3.89) pg/ml. A virological study continued to record a negative HCV PCR RNA in 52.00% of people. The remaining patients $((28.00 \pm 8.92)\%)$ experienced a decrease in viral load, while in 3 patients, a reduction of 1 log was observed, and in 4 patients, a decrease of 2 logs. In patients of 2 groups after six months of treatment in 2 people (8.00 ± 5.33) , increased cytopenic syndrome, which did not allow continued AVT. But all other patients in this group $((92.00 \pm 5.33)\%$ of people) completed antiviral treatment after 48 weeks. Moreover, over the next six months, a stable biochemical response was observed in patients of this group. Assessment of interferon status after 12

months showed further stimulation of the level of endogenous α -IFN ($p < 0.02$). This situation may explain the results of the analysis of virological load in patients in whom HCV PCR RNA continued to be determined ($36.00 \pm 9.55\%$). All patients had a decrease in HCV RNA level by at least 2 logs. Virological response after 12 months continued to be recorded in 56.00% of patients in this group. Thus, the use in the complex treatment of patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease, mineral waters, and vibrotherapy causes the development of a stable biochemical response, eliminates the side effects of AVT as flu-like and cytopenic syndromes, and stimulates interferonogenesis.

Conclusions.

1. The use of silicon low-mineralized sodium bicarbonate MW and vibroacoustic therapy in complex treatment helps to significantly reduce the clinical signs of the disease ($p < 0.001$), eliminate the cytotoxic syndrome and cholestasis ($p < 0.001$), which occurred against the background of the restoration of ultrasonographic parameters of the pancreatobiliary system.
2. It is proved that vibroacoustic therapy eliminates the manifestations of the flu-like syndrome and eliminates the signs of cytopenia (leukocyte and thrombocytopenia), which allowed to complete the course of antiviral therapy in 92.00% of patients of group 2.
3. The ability of vibroacoustic therapy to stimulate endogenous interferonogenesis has been proven, which made it possible to obtain a virological response in 56% of patients in this study and to reduce the virological load in other patients by at least 2 logs.

Prospects for further research.

After the elimination of the hepatitis C virus, there remains a high risk of further progression of liver fibrosis, which is associated with the preservation of NAFLD in the majority of examined patients. This circumstance stimulates us to continue our scientific research and develop new methods of internal use of mineral water and the use of other physiotherapeutic methods.

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