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ADIPONECTIN CORRELATION WITH BIOCLINICAL BENEFITS OF USING NATURAL THERAPEUTIC FACTORS IN KNEE OSTEOARTHRITIS

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Abstract

Context and objective. The new insights in the pathogenesis of osteoarthritis (OA) reveal the implications of adipocytokines. This study aims to analyze the correlations between the serum value of adiponectin and the clinical rehabilitation effects in patients diagnosed with knee OA, admitted and treated in the complex balneal resort of Techirghiol lake.

Subjects and methods. The prospective randomized clinical study included 23 patients in the study group, diagnosed with knee OA according to ACR criteria, and a matching control group of 23 subjects. Serum level of adiponectin (using ELISA technique), uric acid, triglycerides, cholesterol, HDL-cholesterol and clinical response using a visual analog scale (VAS) were evaluated in all patients on their admission day and after 10 days of balneal treatment. Control group benefited from the same procedures except for cold mud therapy and mineral water baths.

Results. Plasma adiponectin levels (23.73±6.44 ng/dL) were statistically higher ($p<0.05$) in the study group compared to the control group (18.15±6.49 ng/dL). The mean VAS in both groups was decreased ($p<0.005$) compared to the initial moment.

Conclusions. Cold peloidotherapy combined with physical therapy and balneal factors induces serum adiponectin elevation and improves knee pain in OA. Therapeutic properties of Techirghiol mud still need further research.

Key words: adiponectin, osteoarthritis, mud, knee, VAS, Techirghiol.

INTRODUCTION

In the past years, in medical literature, emphasis has been placed on implication of adipocytokines in inflammatory processes of the osteoarticular system as well as in osteoporosis (1). Both white and brown adipose tissue is producing interleukin (IL)-1 β, tumor necrosis factor (TNF)- α, IL-6, IL-8, IL-17, basic fibroblast growth factor, vascular endothelial growth factor (VEGF), leptin, resistin, adiponectin and probably many others.

Infrapatellar fat pad (IPFP), fat tissue situated intracapsular and extrasynovial in the knee joints, rich in vessels, nerve fibers, immune cells, produces all the above mentioned adipocytokines which can play a role in the initiation and progression of knee osteoarthritis (2, 3).

OA is a multifactorial degenerative joint disease characterised by damaged articular cartilage, modified subchondral bone architecture, formation of bone exostosis and inflammation of the synovia.

Even if OA is the most common so-called "non inflammatory" rheumatic disease, according to new research, inflammation plays an important role in its etiology, along with obesity, age, previous injuries etc. (4, 5).

In the last years, balneological research was directed towards the study of specific inflammatory cytokines involvement in musculo-skeletal disorders. Correlations between peloid therapy and inflammatory pathways, at molecular level, are established and new insights in the world of chondrocytes and osteoblasts are brought to light (6).

In general, adiponectin is considered a benefic adipokine because of its systemic anti-inflammatory effect based on reduction of T cell activation, of the seric levels of IL 6 and TNF-α, of its antiatherosclerotic properties etc. (7).

Medical data is contradictory regarding the role of adiponectin in osteoarticular disorders. There is proof that adiponectin decreases both in the serum and in synovial fluid along with the aggravation of OA (8) and also with the radiologic deterioration of hand OA. (9). Contrary to all that, there are other opinions

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that adiponectin is involved in the pathogenesis of OA with a proinflammatory effect at chondrocytes level and also in the degeneration of interstitial cartilaginous matrix (10-12). In chondrocytes, *in vitro*, this adipokine induces pro-inflammatory mediators such as nitric oxide, IL-6 and matrix metalloproteinase with catabolic effects (13, 14). Furthermore, one study revealed a higher level of adiponectin in the IPFP of the patients with knee OA, especially in advanced stages, than in the subcutaneous tissue (15).

Mud, a balneotherapeutic agent used for centuries, preserves its mysteries regarding its implications in the pathophysiology of osteoarticular system. The complex biochemical composition of Techirghiol peloid, with its rich microbial flora, represents a valuable therapeutic option in musculo-skeletal disorders.

In an already published paper we obtained proof of the influence of warm mud applications over the serum levels of adiponectin in patients with knee OA (16).

This study aims to evaluate the serum level of adiponectin and the rehabilitation benefits using a visual analogous scale for pain (VAS) under the effect of natural therapeutic factors after 10 procedures of cold mud applications (CMA) in knee OA. We also aim to find out if there are any correlations between adiponectin and uric acid, considered a pro-inflammatory articular factor, and if balnear treatment affects adiponectin's cardiovascular protective role, regarding lipid profile.

PATIENTS, MATERIAL AND METHOD

In our prospective randomized clinical study, we included 2 groups: the study group consisting in 23 patients, between 30 and 70 years old, diagnosed with knee OA, according to ACR criteria (17) and a matching control group of 23 patients. The patients were hospitalized in the Balnear and Rehabilitation Sanatorium of Techirghiol between 01.06.2016-01.09.2016.

All subjects signed a special informed consent with the agreement to participate in this study and approval of the sanatorium ethical committee was obtained.

Patients from the study group (cold mud applications group-CMAG) performed 10 complex physical and balnear therapy procedures, in Techirghiol specific area, consisting in hydrotherapy (general cold mud baths and salt bath in the lake Techirghiol), heliotherapy, electrotherapy (current of low, medium, high frequency, laser therapy, ultrasonotherapy, phototherapy), massage therapy, kinesiology; while the patients in control group (CG) performed the same therapy except for specific hydrotherapy (mud baths or salt baths in Techirghiol lake).

Serum adiponectin, uric acid, cholesterol, HDL-cholesterol, triglycerides and clinical response after natural treatment with sapropelic mud were evaluated in all patients as follows. All patients were evaluated on their admission day and after 10 days of balnear treatment. Blood samples were collected at admission, before treatment and at discharge, both determinations respecting an overnight 12 h digestive rest. Serum adiponectin was determined at admission and after 10 days of treatment. Specific reagents were used for the determination of human adiponectin using ELISA technique produced by "DRG Instruments GmbH", Germany, with normal reference values of adiponectin according to BMI in Table 1 (however, the producer considered that every laboratory should establish their own values).

Table 1. Adiponectin reference values according to BMI

Gender	BMI (kg/m^2)	Mean (µg/mL)	SD (µg/mL)
Men	< 25	15.9	4.0
	25-30	13.8	4.0
	> 30	13.3	2.8
	Total	14.5	3.9
Women	< 25	18.6	5.4
	25-30	18.9	8.6
	> 30	16.4	3.8
	Total	18.2	6.1

In parallel, the groups were analyzed in terms of age, gender, average age of the disease, body mass index and severity of pain in the knee joints assessed by visual analogue scale (VAS).

Exclusion criteria were: patients with erythrocyte sedimentation rate (ESR) > 40 mm/h; patients with skin disorders (chronic or acute), including skin lesions; with serious conditions such as: cardiovascular, respiratory, digestive, renal, neurological; cancer; presence of connective tissue disorders, pregnancy. Previous treatments were restricted as follows: Nonsteroidal Antiinflammatory Drugs (NSAIDs) and steroids at least 4 weeks before study entry; surgery (arthroplasty, arthroscopy, abrasion, etc.) performed at least 3 months before the study; administration of corticosteroid intra/periarticular at least 6 weeks before starting the trial or hyaluronic acid with at least 6 months before the study; treatment with opioids for at least 4 weeks before study

entry; physiotherapy, acupuncture, transcutaneous electrical nerve stimulation (TENS), massage and physical therapy at least 4 weeks before study entry; administration of sedatives, hypnotics, anticonvulsant and muscle relaxant at least 2 weeks before study entry.

Statistical interpretation of the results was performed by processing data using IBM SPSS 18.0. The results were analysed with mathematical methods in order to obtain an average of the values, standard deviation and also the standard error of the media (descriptive statistics in order to characterise discrete and defined continuous variables); parametric statistical tests (t-Test to compare media of two independent samples and t-Test to compare media of paired samples).

Normal distribution was confirmed for all studied variables by Shapiro-Wilk test ($p > \alpha = 0.05$). By assessing Skewness and Kurtosis coefficients resulted that distributions are symmetrical and they do not present an abnormal vaulting.

Correlations were considered according to the values of the r correlation coefficient (adapted after D.E. Hinkle, W. Wiersma si G.S. Jurs, 1988, p.118).

The values of adiponectin, VAS, cholesterol, HDL-cholesterol, triglycerides, uric acid measured in the first day of treatment were registered as "Adiponectin 1", "VAS 1" etc. At the end of treatment, after 10 days of balneotherapy, the values were registered as "Adiponectin 10", "VAS 10" etc.

Statistical measurements were presented in Table 1.

RESULTS

Presentation of the study groups

The two groups contained 23 patients each and were considered statistically similar in terms of demographic features and of associated co-morbidities, such as metabolic syndrome and diabetes which might have had an impact over adiponectin values (18).

- sex (60.9% females in CG, 65.2% females in CMAG, p>0.05),

- age (medium value in CG=56.17±12.2 years *vs*. 55.17±8.28 years in CMAG, p=0.747>0.05),

- medium value of BMI (29±4.64 in CG *vs*. 27.69±4.33 in CMAG; p=0.328>0.05),

- medium value of VAS scale at admission (5.43±2.52 *vs*. 5.45±1.87, p=0.974>0.05),

- values of adiponectin 1 (17.90 ±8.04 ng/dL in CG *vs*. 20.24±9.90 ng/dL in CMAG, p=0.198>0.05). Adiponectin values were correlated with BMI in both groups (p <0.001, r = -0.690, negative correlation in CG and p = 0.002, r = -0.609, negative correlation on CMAG),

- values of glycemia in day 1 (CG: medium value 111.60 ±19.21 mg/dL *vs*. 118.52±34.20 mg/dL, p = 0.40>0.05,

- proportion of diabetic patients (considered both from anamnesis and after a cut-off value of glycemia of 126 mg/dL, twice registered) was 21.7% in CG *vs*. 26.1% in CMAG, ($\lambda 2$=0.00, p>0.05),

- length of disease (in CG: 8.7% of the patients had a duration of 1-6 months, 17.4% had a duration of 6-12 months, 43.5% had a duration of 1-5 years, 13% had a duration of 5-10 years and 17.4% of more than 10 years, in the CMAG the percentages are: 4.3%, 13%, 52.2%, 17.4% and 13 %. All proportions compared revealed a p>0.05),

- regarding the presence of metabolic syndrome the control group was statistically similar with the study group ($\lambda 2$ =0.392; p>0.05),

- both cholesterol and HDL –cholesterol and uric acid values did not differ significantly between groups.

We divided time of illness in the following time intervals: 1 – 6 months, 6 months – 1 year, 1 to 5 years, 5 to 10 years and more than 10 years. Occurrence of pain was considered the time of OA onset (the main feature of knee OA). We found that the patients suffering from pain for 1 up to 5 years were in a bigger number than in the other time intervals.

In CMAG, adiponectin 10 (23.73±6.44 ng/dL) is significantly higher than in day 1 (20.24±9.90 ng/mL) (t = -2.919; df = 22; Mdiff = -3.482; p = 0.008).

The difference between adiponectin 10 in CMAG and the one in CG was significant, also, in favor

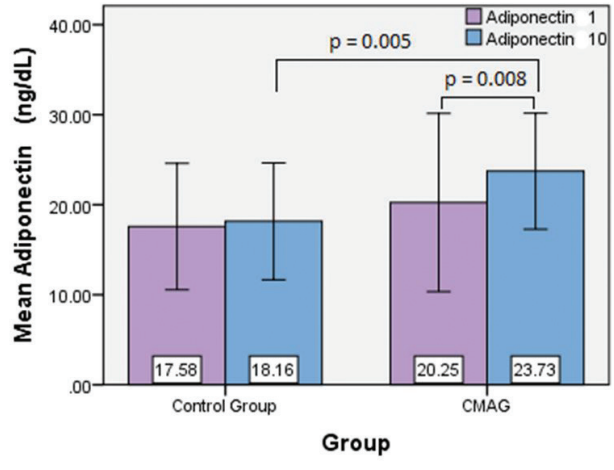

Figure 1. Values of Adiponectin 1 and 10 in both groups.

of the CMAG (t = -2.922; df = 44; Mdiff = -5.573; p = 0.005), see Figure 1.

We found no statistical difference between the values of adiponectin 1 and adiponectin 10 in CG (17.58±7.02 ng/mL *vs*. 18.15±6.49 ng/dL; t = -0.461; df = 22; Mdiff = -0.573; p = 0.649>0.05).

Adiponectin significant negative correlation with BMI persists in the 10th day of treatment.

VAS, a tool for measuring subjective pain that cannot be measured directly, was performed both in the research project baseline, day 1, and after 10 days of treatment.

VAS 10 in CG is 3.93±2.30 while VAS 10 in CMAG is 3.76±2.10.

Even if the difference between VAS 1 and VAS 10 is significant in each group (t = 4.657; df = 22; Mdiff = 1.5; p < 0.001 in CG, t = 6.28; df = 22; Mdiff = 1.69; p < 0.001 in CMAG), there is no difference between VAS 10 in CG and the one in CMAG (t = -0.267; df = 44; Mdiff = 0.17; p = 0.791).

In our study, VAS 10 had a significant negative correlation with adiponectin 10 value only in the CMAG (p = 0.036< α = 0.05, r = -0.44, considered a mild correlation).

DISCUSSION

The variety of the natural therapeutic agents used in balneotherapy, the influence of seasons and of the climate - different from the one of the patients' residence place, and of the changes in diet and daily activity, make strong scientific studies difficult in the field of balneology. Because of all that, debate exists in medical literature regarding the benefits of mud therapy.

In our study most of the patients were suffering from knee pain for 1 up to 5 years. It seems that patients with symptoms for less than 1 year are underestimating the knee OA evolution and prognosis, while those with more than 5 years of suffering are somehow "adapted and consoled" with the situation.

VAS is a psychometric response scale that can be used in questionnaires. It is a tool for quantifying subjective characteristics or attitudes that cannot be measured directly. When responding to a VAS item, respondents specify their level of agreement to a statement that indicates a position along a continuous line between 2 end points (pain with intensity from 1 up to 10, for example). In our study VAS was significantly lower on the 10th day of treatment in both groups. This is, once more, the proof of balneal treatment efficiency in knee osteoarthritis.

Our study brings proof not only of mud therapy efficiency but also of its possible correlations with adiponectin.

Adiponectin, an adipocytokine discovered in 1995, produced by adipocytes synthesis in many forms: low-molecular weight trimers, medium and high-molecular weight trimers, plays an important role in metabolic regulation and in inflammatory/anti-inflammatory processes. Among these, adiponectin enhances 5' AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPARα) pathway in the striate muscle and in the liver, prevents insulin resistance by increasing fatty acids oxidation, offers cardio-vascular protection by augmenting the endothelial nitrous oxide production and reducing platelet aggregation, while its reduction seems to increase the risk of coronary heart disease, steatohepatitis, insulin resistance (19) as well as of biliary sludge and lithiasis (with similar contribution as other risk factors: pregnancy, parity, dyslipidemia etc) (20, 21).

If up to 5-6 years ago, medical data sustained the pro-inflammatory effect of adiponectin, with a deleterious effect over the cartilage (22-24) and just a few considering that adiponectin may have a protective role in the progression of OA, proving that both the serum and the synovial level of adiponectin decrease significantly with the severity of osteoarthritis (25), or that adiponectin modulates cartilage destruction in chondrocytes (up-regulating TIMP-2 and down-regulating IL-1beta- induced MMP-13) (26), new studies (27-29) are sustaining the beneficial effect of adiponectin over joint cartilage. Under the same light, the study of Zheng S *et al.* published in 2016 in Scandinavian Journal of Rheumatology sustaines that serum adiponectin is significantly and negatively associated with radiologic severity of knee osteoarthritis (30).

Looking at our results, we found a statistically significant variation of adiponectin after 10 days of complex balneal therapy in the study group compared to control group. Cold mud bath induced a significant increase in serum adiponectin values both related to value of adiponectin 1 in CMAG and to the adiponectin 10 of the control group. Based on our previous study, in which we found that hot peloid bath induced significant decrease in serum levels of adiponectin value after 10 days (16), we suppose that thermoregulation interferes with therapeutical results of peloid baths, along with other similar results from medical literature (31, 32). This is why we will extend our study with repeated

dosage of serum levels of adiponectin at 3 months/ 6 months after balneal contrastant treatment, because we have a new work hypothesis.

By excluding the possibility of a pregnancy, in fertile patients, we, first, reduced the necessary investigations, some of them being rather specific for our region (33). We have, also, took care of the possible adverse effect of anticonvulsant therapy – even before the 4 weeks prior the beginning of the study (34). A possible effect of the cortisol, due to high estrogen levels (35) was also avoided.

We did not find a significant correlation between adiponectin values and the levels of uric acid, HDL-cholesterol, triglycerides in either group.

The results of this study, that adiponectin values are higher in case of cold mud applications than in the control group, are in contrast with our previous results (16), in which hot mud baths reduced the value of adiponectin. At the same time the significant negative correlation between VAS scale and adiponectin level is pleading for a protective role of adiponectin over knee osteoarthritis. So, we consider that thermoregulation is involved, and further research is needed to establish the relation between adiponectin, reduction of pain and cold peloid treatment with Techirghiol mud.

In conclusion, although the study included a small number of cases, it allowed the issuance of plausible assumptions on understanding the beneficial effects of Techirghiol peloid on osteo-articular degenerative disorders.

In our study we find a significant elevation of adiponectin level after 10 cold sapropelic mud applications in the study group as related to the control group.

Even if prevention of obesity related to pro-inflammatory cytokines' production is still relying on physical activity, reduction of fat body mass and healthy diet, new data about control of adipokines and their effect over osteoarthritis may represent the base of new pharmacological approaches in this disease.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contribution

Ionescu Elena-Valentina and Tica Irina equally contributed to this article.

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Anatomic-Imaging Correlations of Lumbar Disk-Vertebral Morphometric Indices

Correlaciones Anatomopatológicas de los Índices Morfométricos Disco-Vertebral Lumbar

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ILIESCU, D. M.; BORDEI, P.; IONESCU, E. V.; ALBINA, S.; OPREA, C.; OBADA, B.; LUPU, A. A.; HANGAN, T. L. & ILIESCU, M. G. Anatomic-imaging correlations of lumbar disk-vertebral morphometric indices. *Int. J. Morphol., 35(4)*:1553-1559, 2017.

SUMMARY: This study represents a morphometric assessment of the anterior segment of the lumbar spine, focused on the vertebral body - intervertebral disk assembly, calculating some specific indicators and then completing direct morphometry data with the data resulting from the imaging interpretation and subsequently correlating the same to map an anatomic-imaging model. The study was carried out with anatomic items from personal archive and images obtained from Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) assessment. The morphometric assessment was carried out for intervertebral disks, the disk height in the anterior and posterior sections and correlated with the disk angle degree. Direct morphometric data was compared and correlated with the data resulting from the imaging interpretation. Direct morphometric assessment was carried out for 11 vertebral blocks; the vertebral blocks were sectioned and turned into 22 vertebral semi-blocks allowing easy access to absolutely all dimensional values pursued, including the ones covered by the posterior arc. The assessment of imaging data was made with CT, CT 3D and MRI investigations from the 120 subjects in the study. The disk sizes were assessed by direct measurements on the anatomic items and directly measured by means of the software for modern imaging examination. In case of significant differences between the vertebral bodies, the calculation of disk sizes was made indirectly, on grounds of the geometric interpretation of the vertebral body face sizes. The vertebral body / intervertebral disk (IVD) assembly represents a dynamic structure, permanently subject to changes and adaptation, IVD being capable of incurring changes for the entire life time, including growth changes; the growth, however, is not lineal, but a succession of thickening and getting thinner, in full concordance with the structural stresses and changes occurring inside.

KEY WORDS: Lumbar spine; Direct morphometry; Vertebral blocks.

INTRODUCTION

This study represents a morphometric assessment of the anterior segment of the lumbar spine, focused on the vertebral body - intervertebral disk assembly, calculating some specific indicators and then completing direct morphometry data with the data resulting from the imaging interpretation and subsequently correlating the same to map an anatomic-imaging model (Panjabi *et al*., 1992; van der Houwen *et al*., 2010).

MATERIAL AND METHOD

The study was carried out with anatomic items from personal archives and images obtained from CT and MRI imaging assessment. The morphometric assessment was carried out for intervertebral disks, the disk height in the anterior and posterior sections and correlated with the disk angle degree (Nissan & Gilad, 1986; Aharinejad *et al*., 1990; Iliescu *et al*., 2006). The morphometric indices calculated were: the relative disk-vertebral index, respectively the disk height - intervertebral body height ratio and the disk-vertebral angle index (wedge index), respectively the angle between the vertebral body sides corresponding to the disk angle degree. Direct morphometric data was compared and correlated with the data resulting from the imaging interpretation. Direct morphometric assessment was carried out for 11 vertebral blocks; the vertebral blocks were sectioned and turned into 22 vertebral semi-blocks allowing the easy access to absolutely all dimensional values pursued, including the ones covered by the posterior arc (Fig. 1).

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The assessment of imaging data was made with CT, CT 3D and MRI investigations from the 120 subjects in the study (Fig. 2).

All direct measurements were performed by means of a digital meter, with a 0.01 mm calibration level and introduced in formulae, while the assessment of CT 3D and MRI images, the dimensional calculation and the angle calculation could be directly achieved with the implemented software (Cramer *et al*., 1994; Silva *et al*,. 1994; Zhou *et al*., 2000; Edmondston *et al*., 2000).

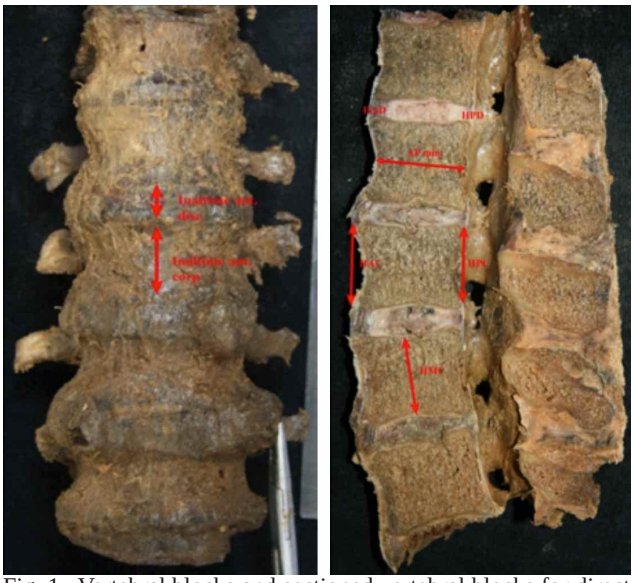

Fig. 1. Vertebral blocks and sectioned vertebral blocks for direct morphometric data (personal archive).

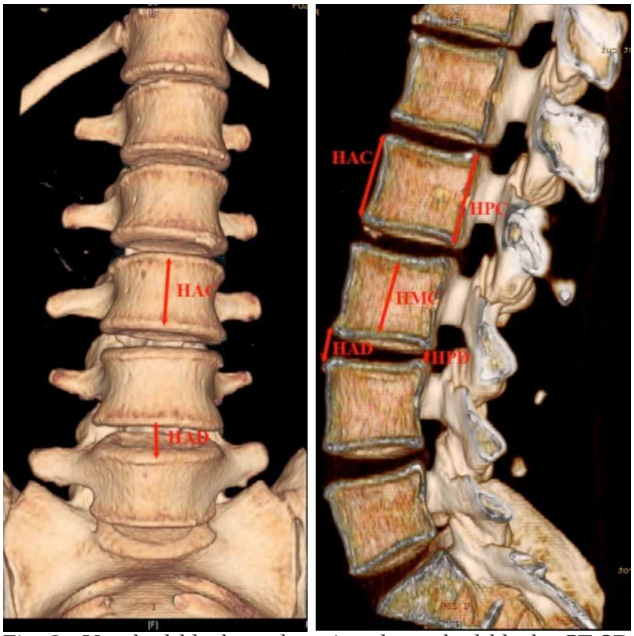

Fig. 2. Vertebral blocks and sectioned vertebral blocks CT 3D reconstructed images (personal archive).

RESULTS AND DISCUSSION

The disk sizes were assessed by direct measurements (Fig. 3) on the anatomic items and directly measured by means of the software for modern imaging examination.

In case of significant differences between the vertebral bodies, the calculation of disk sizes was made indirectly, on grounds of the geometric interpretation of the vertebral body face sizes (Eijkelkamp, 2002). Thus, we started from marking the extreme contact points between the body and the disk, represented by the most protruding vertebral points in the direction of the intervertebral disk, a, b, c, d, as well as the half distances a-b and c-d, respectively, which distances represent the anterior-posterior maximum diameters of adjacent vertebrae. The height of intervertebral disk is obtained with perpendicular lines drawn through the extreme points to the medial-sagittal line, respectively by adding the halves so obtained (A + A', M + M', P + P') (Fig. 4).

Specifically, the imaging assessment allowed the average values of the intervertebral disk height to be recorded according to sex and age groups (Twomey & Taylor, 1987; Scoles *et al*., 1988). The average values of the intervertebral disk heights and the evolution of anterior and posterior heights of the lumbar intervertebral disk for the lumbar region obtained by imaging assessment are presented in Figure. terms (Table I, Fig. 5).

Table I . Average heights of intervertebral disks per lumbar levels, obtained by direct measurement

	Anterior height	Posterior height	Average
L1-L2	10.71	5.1	7.91
L2-L3	13.16	6.14	9.65
L3-L4	15.55	7.05	11.30
L4-L5	17.81	7.68	12.75
L5-S1	16.92	7.14	12.03

Both values distributions show a more than significant correlation level, respectively R2 = 0.9754 and R2 = 0.9131, thus demonstrating the statistical certainty of the assessment. Figure 6 show the evolution of intervertebral disk height during three decades of active life, respectively 30-60 years.

We can assess that, at the upper levels of the lumbar segment, the evolution is relatively uniform, while the highest dimensional variations are recorded at the inferior

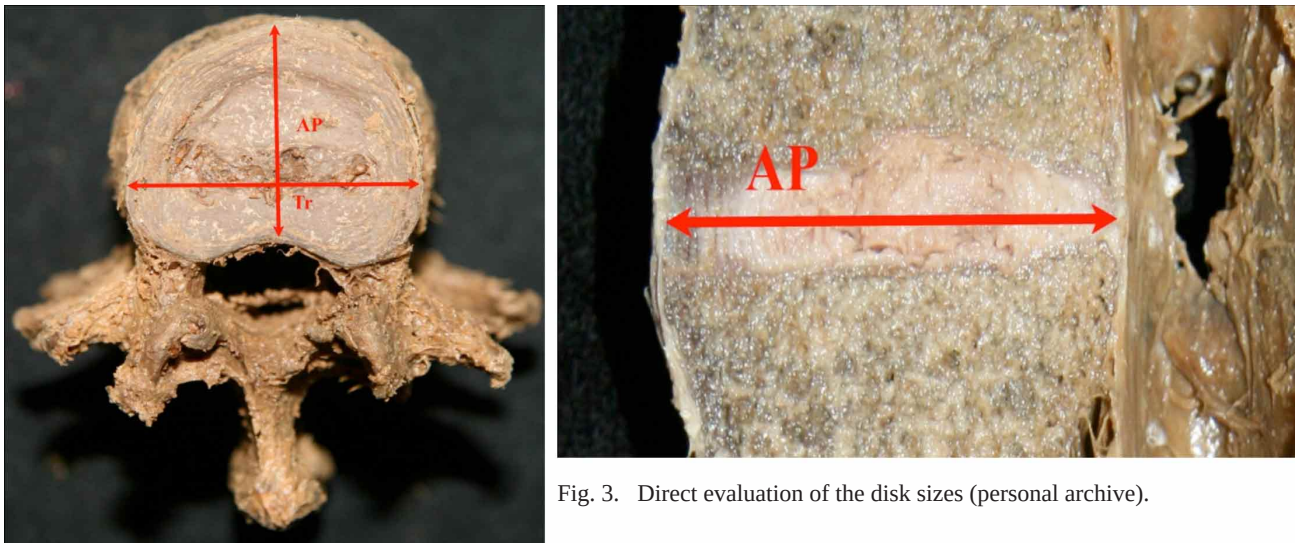

Fig. 3. Direct evaluation of the disk sizes (personal archive).

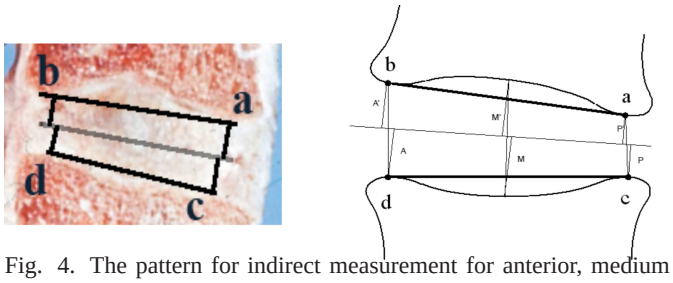

Fig. 4. The pattern for indirect measurement for anterior, medium and posterior height of intervertebral disk (Eijkelkamp)

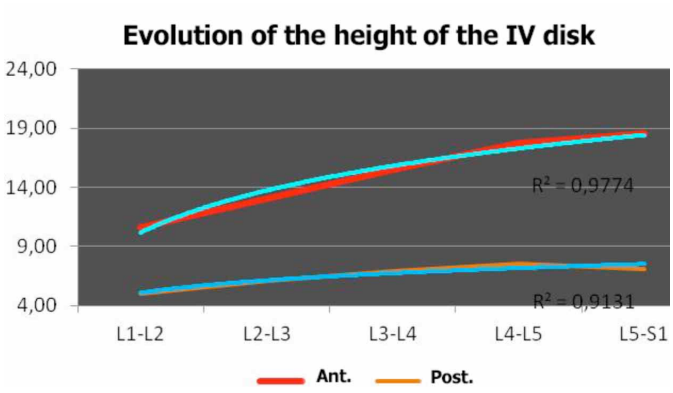

Fig. 5. AHIVD and PHIVD = anterior and posterior heights of intervertebral(IV) disk.

levels, L3 - L4 and L4 - L5. A higher disk at active ages is a bio-mechanical win, however, for the same disk, at older ages, it will have no advantage, on the contrary it may actually turn into a pathological issue if the IVD structural and composition changes are considered in time.

The most efficient and convenient method to assess and express the angles formed by the adjacent faces of vertebral bodies, respectively the disk angle, is represented by the measurement by means of modern imaging software (Cramer *et al.*), such as MRI and / or CT 3D, which software, if well calibrated, provides high accuracy data in real time at high speed (Fig. 7).

The IVD height reduction in time is a structural certainty, largely explained by the degenerative changes occurring at this level.

In Table II are represented the differences of absolute values from anatomic and imaging measure, given by the presence of surrounding tissues (soft tissues, ligaments, minor osteophytes, etc.); the low value of the anatomic-imaging variation coefficient, however, confirms the morphometric accuracy level of imaging methods, for which reason imaging is self-sufficient as superior method, especially modern methods allowing fine assessments and calibrations.

For a better representation of the relations between the various structural elements in the region and, especially, to describe the body-disk assembly, the absolute dimensional values can generate useful morphometric indices illustrating more efficiently the specific region aspects, easier to handle and, at the same time, report the existing data in the literature (Table III).

We also calculated two specific indicators for the vertebral body / intervertebral disk assembly, namely: the relative disk-vertebral index and the disk-vertebral angle index. The relative disk-vertebral index (R.I), respectively the disk height-body height ratio (Brandner, 1970; Amonoo-Koufi, 1985, 1991; Aydinlioglu *et al.*, 1999), adds to the disk-vertebral angle degree attempting

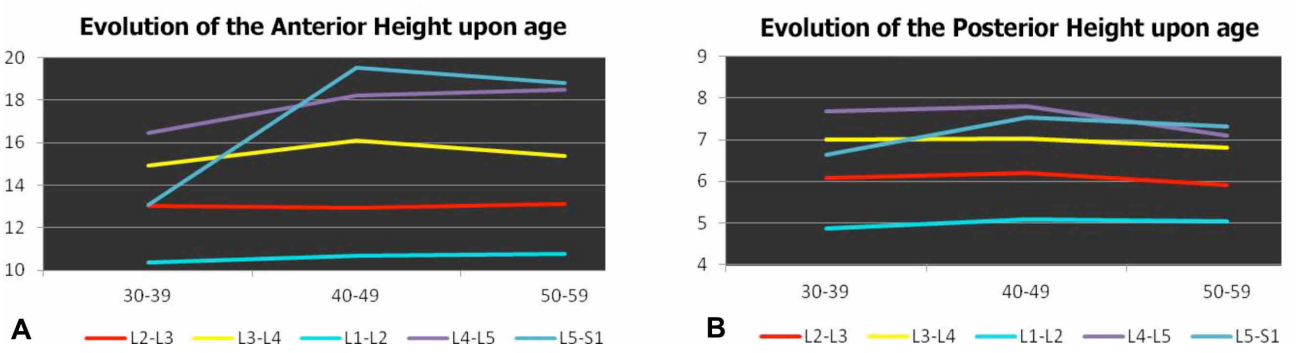

Fig. 6. A and B. Age evolution of anterior and posterior height IVD.

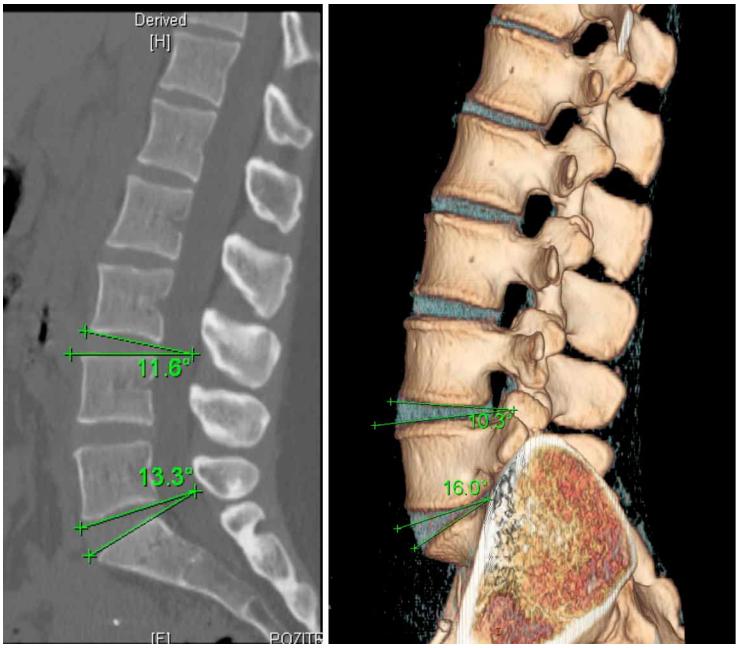

Fig. 7. Wedge (disk) angle- classic CT and CT 3D (personal archive).

to complete as precisely as possible the image of dimensional ratios between the body and the disk and obtaining the ratio between the sum of intervertebral disk heights (AHIVD and PHIVD) and the sum of corresponding vertebral bodies heights (AHV + PHV). R.I = AHIVD + PHIVD / AHV + PHV. By its calculation method, the relative disk-vertebral index represents the parameter most faithfully monitoring the changes liable to occur in the functional assembly disk / body, for which reason it is recommended to quantify it in evolution. Another argument in the favor of this assertion is that the change of the relative disk-vertebral index can be induced, especially in degenerative situations, from dimensional variations at the intervertebral disk level (more frequently) and at the level of the vertebral body (seldom, but not impossible). As compared to some data in the literature, the values obtained by the study are lower than the data of other authors (Table IV), between 3.99 and 8.75 %, such differences being explained by the fact that both authors used the maximum values of the height of the body and the corresponding disk. This is also confirmed by the similarity with the results provided by Amono-Kuofi for 615 cases applying a similar calculation formula.

We consider that the values we obtained are more reliable in reference to dimensional ratios between the vertebral-disk elements than the ones obtained by the old formula, namely the direct ratio of the intervertebral disk height and the corresponding vertebral body height. An issue to be noted is the one concerning the relative index distribution per age groups (Fig. 8).

Clinical studies (Iliescu *et al*., 2009, 2012; Niosi *et al*., 2004; Turk & Celan, 2004) showed an increase in the idiopathic low back pain incidence at young and active ages (little over 30 years old), when the physical activity can be significant; this age involves multiple factors which can derive from a relatively lower height of the intervertebral disk, as well as congruence issues of joint apophyses, posterior longitudinal ligament relaxation, etc. The increase of the relative index in decades 5 and 6, obviously due to the IVD height increase can add to the correction of such deficits, the hypothesis, further being supported by the clinical studies confirming some improvement of the symptoms in time.

Disk-vertebral angle index (wedge index-WI). The dimensional values of the vertebral body and intervertebral disk can be globally and highly suggestively expressed by the disk angle (wedge index) and must not be mistaken for the vertebral-disk angle (Aharinejad *et al*.; Eijkelkamp; Aydinlioglu *et al*.; Amono-Kuofi; Gepstein *et al*., 1991). There are two methods to calculate this index:

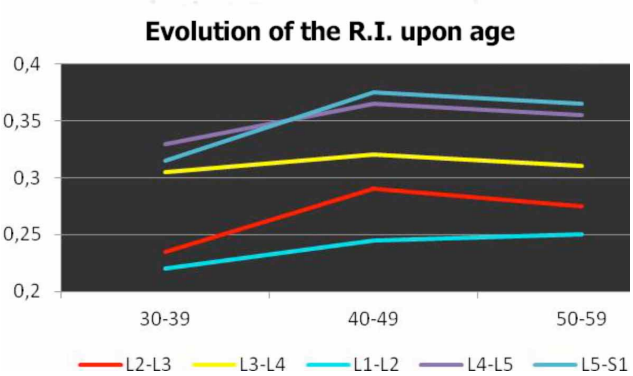

Fig. 8. The relative index distribution per age groups.

Table II. Absolute values and anatomic-imaging variation coefficients for the vertebral-disk angle

Level	Direct	Imagistic	Variation coefficient
L1-L2	5.8	5.2	1.12
L2-L3	6.2	5.9	1.05
L3-L4	7.1	76.8	0.09
L4-L5	10.2	9.7	1.05
L5-S1	13.4	12.8	1.05

- calculation according to the formula AHIVD - PHIVD / APD, where APD represents the maximum anterior-posterior disk diameter (AHIVD and PHIVD are the anterior, respectively posterior height of the disk);
- calculation according to the formula sin-1 x (AHIVD - PHIVD) / 1/2 (SD + ID), where SD and ID are the superior, respectively inferior diameters of the vertebral faces adjacent to the disk.

It is interesting the manner in which this "wedge index" evolves per age groups, for each lumbar level (Fig. 9).

A brief analysis of the value distribution per age groups will show that, similarly to the other indices, the disk-vertebral angle index also, for the inferior level L3 -L5 is the one recording the most significant changes. Also, starting with the 5th decade, the trend of this index is to stabilize, the trend being explained by the structural changes occurring in the body-disk assembly (Twomey & Taylor; Scoles *et al.*). The vertebral-disk angle index has special effects, both in physiological and pathological terms. The vertebral-disk angle is the one imprinting the lumbar spine lordosis level; in case of normal lordosis, the angle of vertebral bodies contributes with approximately 300, and the disk angle with 60. As compared to some literature data, the average value of disk-vertebral angle indices shows as follows (Table V and Fig. 10).

Table III. Average heights of intervertebral disks per lumbar levels, compared to literature.

Level	Personal cases	Campbell *et al.* 2005 (39 cases)	Busscher *et al.* 2001 (6 cases)	Aydinlioglu *et al.* 1999 (200 cases)	Eijkelkamp (73 cases)
L1-L2	7.91	8.4	10.3	8.2	10.2
L2-L3	9.65	9.3	11.5	10.1	12.1
L3-L4	11.30	10.1	11.8	12.1	12.5
L4-L5	12.75	10.5	12.7	13.1	13.7
L5-S1	12.03	9.4	8.8	11.9	13.2

Table IV. Comparative relative disk-vertebral index (RI) (imaging exploration).

Level	Personal cases	Brandner (187 cases)	Aydinlioglu (200 cases)	Amono-Kuofi (615 cases)
L_1-L_2	0.235	0.252 (6.75%)	0.25 (6%)	0.229 (-1.29%)
L_2-L_3	0.2667	0.286 (6.76%)	0.2917 (8.75%)	0.258 (-2.18%)
L_3-L_4	0.3117	0.334 (6.69%)	0.3383 (7.88%)	0.319 (2.29%)
L_4-L_5	0.3533	0.368 (3.99%)	0.375 (5.78%)	0.349 (-1.23%)
L_5-S_1	0.3585	0.379 (5.45%)	0.3783 (5.29%)	0.357 (-0.42%)

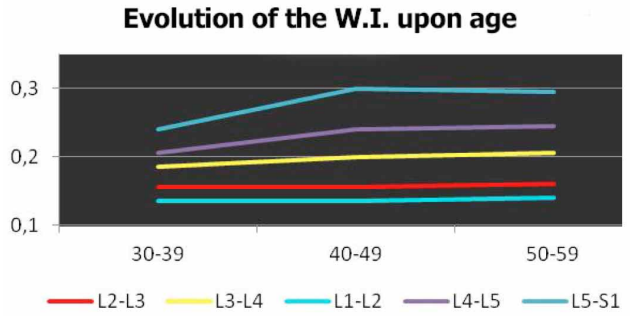

Fig. 9. The wedge index distribution per age groups.

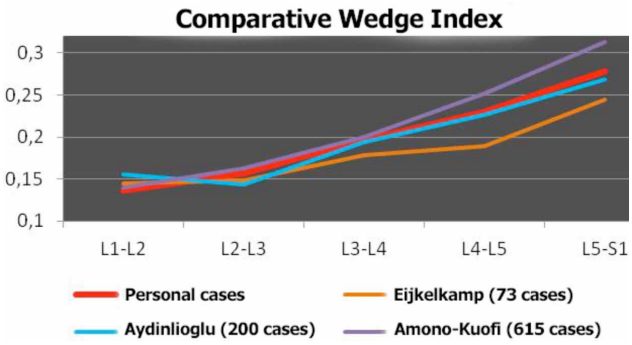

Fig. 10. Disk-vertebral angle index (wedge index), compared to literature.

Both statistically and dynamically, the intervertebral disk is subject to massive stress, not only due to the body weight itself, but also due to the muscle stress, compressive and tensioning, as well as the shearing forces induced by the same muscular jacket (Iliescu, 2011). In such conditions, the disk-vertebra angle becomes a prevention factor for disk protrusion towards the posterior, while a reduction of this index (and, globally, of the lordosis level) becomes a factor entailing disk protrusion, the aspect being confirmed by the literature also.

CONCLUSIONS

The vertebral body / intervertebral disk assembly represents a dynamic structure, permanently subject to changes and adaptation, IVD being capable of incurring changes for the entire life time, including growth changes; the growth, however, is not lineal, but a succession of thickening and getting thinner, in full concordance with the structural stresses and changes occurring inside. Moreover, the intervertebral disk shows cyclic periods of volume changes, directly reflected in the response to stresses. After the 5th decade of life, such changes are lower, directly affecting the adaptation capacity of the intervertebral disk, also. Today we are certain that the disk resistance varies differently according to the level of degeneration, namely we see a reduction in the resistance in the case of moderate degeneration and an increase in stiffness, respectively a reduction of the force absorption power in the case of severe degeneration (Niosi *et al*.; Turk & Celan; Iliescu). The parallelism between the load stress, on one hand, and the disk degeneration, on the other hand, can entail the fibrous ring in a vicious circle invariably resulting in irreversible ruptures at this level.

ILIESCU, D. M.; BORDEI, P.; IONESCU, E. V.; ALBINA, S.; OPREA, C.; OBADA, B.; LUPU, A. A.; HANGAN, T. L. & ILIESCU, M. G. Correlaciones anatomopatológicas de los índices morfométricos disco-vertebral lumbar. *Int. J. Morphol., 35(4)*:1553-1559, 2017.

RESUMEN: El estudio representa una evaluación morfométrica del segmento anterior de la columna lumbar, centrado en el conjunto del cuerpo vertebral - disco intervertebral, calculando algunos indicadores específicos y completando los datos morfométricos directos. El objetivo del trabajo fue mapear un modelo de imagen anatómica con los datos de la interpretación de la imagen, posteriormente correlacionando los datos. El estudio se llevó a cabo con artículos anatómicos de archivos personales y de las imágenes obtenidas de tomografía computarizada (TC) y resonancia magnética (RM) de evaluación. La evaluación

Table V. Disk-vertebral angle index (wedge index), compared to literature.

Level	Personal cases	Eijkelkamp (73 cases)	Aydinlioglu (200 cases)	Amono-Kuofi (615 cases)
L_1-L_2	0,1367	0,145	0,156	0,1400
L_2-L_3	0,1567	0,148	0,0144	0,1633
L_3-L_4	0,1967	0,178	0,194	0,2000
L_4-L_5	0,23	0,189	0,227	0,2517
L_5-S_1	0,2783	0,245	0,268	0,3133

morfométrica se realizó en los discos intervertebrales, la altura del disco en las secciones anterior y posterior y se correlacionó con el grado del ángulo del disco. Se compararon los datos morfométricos directos y se correlacionaron con los datos resultantes de la interpretación de la imagen. Se realizó una evaluación morfométrica directa de 11 bloques vertebrales; Los bloques vertebrales se seccionaron y se convirtieron en 22 semibloques vertebrales permitiendo el fácil acceso a todos los valores dimensionales, incluyendo aquellos cubiertos por el arco posterior. La evaluación de los datos de imagen se realizó en 120 sujetos con CT, CT 3D y MRI. Los tamaños de los discos se evaluaron mediante medidas directas de los elementos anatómicos y se midieron con el software para la examinación de imágenes. En caso de diferencias significativas entre los cuerpos vertebrales, el cálculo de los tamaños de los discos se realizó indirectamente, debido a la interpretación geométrica de los tamaños de la cara del cuerpo vertebral. El conjunto cuerpo vertebral / disco intervertebral (CVDV) representa una estructura dinámica, permanentemente sujeta a transformaciones y adaptación, siendo (CVDV) capaz de incurrir en cambios durante toda la vida, incluyendo aquellos relacionados con crecimiento. El crecimiento, sin embargo, no es lineal, sino una sucesión de engrosamiento y adelgazamiento, en plena concordancia con las tensiones estructurales y los cambios que se producen en su interior.

PALABRAS CLAVE: Espina lumbar; Morfometría directa; Bloques vertebrales.

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Review Article

Autologous Platelet-Rich Plasma Efficacy in the Field of Regenerative Medicine: Product and Quality Control

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Platelet-rich plasma (PRP) has emerged as a significant regenerative therapy used alone or combined mainly with stem cells, autologous fat grafts, hyaluronic acid, and biomaterials in a variety of medical fields, especially in hair regrowth, wound healing, and sports and rehabilitation medicine. However, the results obtained with this biologic therapy are heterogeneous and conflicting. The observed disparities in the effectiveness of PRP therapies may be due to a lack of standardization in blood processing and preparation. This article is aimed at reviewing the main biological parameters that need to be documented for a thorough reporting of quantitative and qualitative characteristics of the PRP injected, to allow a comparison between the quality of samples and the clinically obtained results and advance the efforts towards treatment standardization.

1. Introduction

Platelets (PLTs) are multitalented cells that represent a great reservoir of growth factors (GFs) such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-(TGF-) beta, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF) [1]. All these growth factors are valuable tools in regenerative medicine, due to their different functions and involvement in mechanisms that aim to restore and regenerate human tissue, such as angiogenesis, fibroblasts proliferation, or extracellular matrix development.

PLTs are activated with tissue injury, through exposure to substances such as thrombin and tissue collagen, and activation leads to the release of inflammatory and growth factors, with the potential of initiating and enhancing natural tissue recovery [2]. Platelet-rich plasma (PRP) is an autologous blood-derived biologic therapy, which is reported to deliver supraphysiologic concentrations of growth factors and other signaling molecules locally at the site of tissue injury, thus intensifying the body's healing efforts [3].

Due to its biological properties, this therapy gained huge popularity among a variety of today's medical fields, with the highest level of evidence in hair regrowth [4], wound healing [5], and sports and rehabilitation medicine [6, 7]. But despite its growing popularity, there is a huge controversy whether the theoretical capacity of the PRP therapy to promote and enhance host cellular regeneration does eventually translate into clinical benefit.

There is a growing need to better understand how PRP works and its benefits so that treatments can be optimized and applied appropriately. This article is aimed at reviewing

the main issues creating the gaps between the theoretical effects of PRP therapy and the conflicting clinical results obtained in clinical practice.

2. PRP Use in Hair Regrowth, Wound Healing, and Sports and Rehabilitation Medicine

2.1. Hair Regrowth. In the past years, accumulating data have shown that PRP may represent a valid regenerative strategy for hair regrowth.

In 2014, Cervelli et al. were the first to perform a histomorphometric analysis on the results obtained by three cycles of injections with autologous activated platelet-rich plasma (AA-PRP) in patients affected by androgenetic alopecia, a progressive and chronic hair loss disorder. It was shown that PRP injections increase the thickness of epidermis and the number of follicles of hair skin, improve the blood supply around the hair follicles, and increase the proliferation of epidermis basal cells and hair follicular bulge cells, thus promoting hair regeneration in androgenetic alopecia [8].

In a randomized, controlled trial published in 2017, Gentile et al. compared the effects of nonactivated PRP versus calcium-activated PRP in hair loss treatment, and both options have proved similar hair density improvements, despite the higher concentration of growth factors (PDGF-BB, TGF-β1, and VEGF) depicted in the activated PRP [9]. In the same paper, the authors introduced the possibility to inject the PRP by using a medical injector gun, to precisely control both the delivered dose and the depth of the injection [9, 10].

In 2017, Gentile et al. also published the first paper about the clinical use of autologous micrografts enriched with human hair follicle stem cells (HFSCs), without enzymatic digestion, for the treatment of androgenetic alopecia and hair loss [11]. The reservoir for adult stem cells in this study was the bulge, which is highly rich in epithelial and melanocytic stem cells. The simple centrifugation of the bulb obtained by two millimeters of punch biopsies from the scalp of the patients lead to the development of a liquid suspension enriched with autologous unexpanded human follicle stem cells. The suspension was later injected into the scalp areas affected by hair loss and showed an up to 29% improvement in the hair density for the treated area and less than a 1% improvement in hair density for the placebo area [11].

Extremely interesting, the results of a recent study by Gentile et al. [12] showed that autologous human follicle mesenchymal stem cells (HF-MSCs) and nonactivated PRP (A-PRP) therapy have similar effects on the treatment of androgenetic alopecia: the study detected a hair density improvement of $29.0 \pm 5.0\%$ hairs/cm^2 after the second infiltration for the HFSC treatment group and an improvement of $28 \pm 2\%$ hairs/cm^2 after the third infiltration in patients treated with A-PRP.

Molecular pathways mediating these clinical effects are not yet fully elucidated. It is known that enhancement of Wnt signaling in dermal papilla cells plays a central role in increasing hair regrowth [13]. Mesenchymal stem cells and PRP therapies seem to promote hair growth mainly by suppressing the release and activation of apoptotic proteins such as Bcl-2 and Akt [14]. In addition, these biological therapies increase the expression of fibroblast growth factor 7 (FGF-7) [15], activate extracellular signal-regulated kinase (ERK) [16], and increase Wnt/β-catenin signaling [17], leading to accelerated cell growth, prolonged anagen phase of hair follicles, and new hair follicles development.

Nevertheless, in a recently published systematic review, both activated and nonactivated PRP were reported to be a safe and effective alternative treatment for hair loss, when compared with conventional therapies such as topical minoxidil or oral 5-alpha reductase inhibitors (dutasteride, finasteride) [18].

2.2. Wound Healing. In the last decade, an exponentially increase has been noticed in the number of clinical trials evaluating PRP therapeutic effects on wound healing and regeneration of soft tissue defects, when used alone or in combination with hyaluronic acid (HA), biomaterials, and fat grafts [19].

The efficacy of PRP used alone for wound healing has been largely reported [20, 21], and in a recently paper by Gentile et al. [22], it was highlighted that each one of the GFs contained in PRP preparations is involved in a specific biomolecular pathway during the healing process of chronic wounds. Furthermore, in an *in vitro* and *in vivo* evaluation, De Angelis et al. [23] reported that combining PRP and HA in a biofunctionalized scaffold caused significant reepithelialization ($96.8\% \pm 1.5\%$ reepithelialization) of chronic diabetic and vascular ulcers, compared to traditional HA dressings alone ($78.4\% \pm 4.4\%$) within 30 days. Another combination widely investigated in clinical practice is the use of PRP mixed with fat graft and adipose tissue-derived stem cells (AD-MSCs), which has shown promising results in promoting and accelerating the healing process of chronic dermal wounds and posttraumatic extremity ulcers [24].

2.3. Sports and Rehabilitation Medicine. In these fields, a number of injectable agents, including glucocorticoids [25], hyaluronic acid derivatives [26], and botulinum toxin [27], have been used for the treatment of various musculoskeletal conditions. In the latest years, platelet-rich plasma therapy has been widely popularized for the local treatment of soft-tissue and musculoskeletal injuries such as osteoarthritis, ligament injuries, muscle tears, and tendinopathies [28].

However, despite the amount of available data to support the use of PRP in the field of regenerative medicine, this treatment method lacks high-quality evidence [29]. Only a small number of controlled trials support its use, whereas the majority of the clinical trials of PRP lack high-quality evidence of the efficacy of PRP treatments and have small sample sizes or high risk of bias [29].

Also, in the available clinical trials, in most of the cases, the PRP obtained product is not properly characterized, and interstudy comparability is limited. PRP is a general denomination describing a therapy that is highly heterogeneous in preparation techniques. This inconsistency leads to a range of variations in the concentration of active substances in the product that has to be injected and therefore may change the biological features and benefits of PRP [30].

3. The Variety of Materials Used for Blood Harvesting Techniques

For the available PRP commercial systems, blood can be collected from the patients with the use of a variety of techniques as follows:

(i) Vacuum blood-collection tubes containing anticoagulants that may be plain tubes or may contain a separating gel that separates the red blood cells from platelets and plasma at the end of the centrifugation process

(ii) Anticoagulant prefilled syringes that can further undergo immediate centrifugation or may be transferred either in a secondary disposable or in an automated device for centrifugation process thus obtaining the final product to inject

(iii) Blood-collection bags prefilled with anticoagulant

In addition to the different techniques used for blood harvesting, these devices are completely different based on the anticoagulant that is used, the volume, the numbers, the times and the speed of centrifugation, removal or not of the platelet-poor plasma (PPP) part, or the need to resuspend the PLTs into the manual devices [22]. Therefore, it is predictable that each device can produce different biological PRP product.

4. Systematic Biological Characterization of the Injected PRP Is Lacking

Maxillofacial surgeon Robert Marx was the first to use PLTs in this field, using a basic clear definition: "PRP is defined as a suspension of platelets in plasma characterized by a platelet concentration which is higher than the concentration of the original blood collected" [31]. This pioneer publication offered a lot of details about the preparation of PRP sample, about platelets counting for each patient, about the isolated growth factors, and provided a very informative conclusion that for autologous plasma to have high healing properties for bone and soft tissue; the platelet levels should reach the concentration of $1{,}000 \times 10^9$/L in 5 mL of plasma.

Beginning with this paper, a growing interest in PRP for therapeutics has been illustrated by the rapid growth in publications on this topic, with over 500 clinical trials relating to "platelet rich plasma" listed on clinicaltrials.gov (March 2021). The number of randomized clinical trials is increasing each year, but there is one big weakness: in most cases, no characterization of the PRP product is available.

We have herein investigated and synthesized the main variables that need to be documented for a thorough analysis of PRP samples (Figure 1).

4.1. The Volume of PRP. This needs to be specified since it is directly affecting the concentration.

4.2. Platelets Increase Factor. The platelet increase factor refers to the platelet concentration increase in PRP product compared with native peripheral blood, and it is thought to primarily influence the PRP efficacy. Manufactures are largely emphasizing that higher platelet increase factor directly correlates with higher PRP efficacy, but this is only partially true. A platelet concentration in PRP lower than in native peripheral blood may be indeed suboptimal and inefficient but, however, too high platelet concentrations (sixfold higher than baseline) may induce an inhibitory effect on osteoblast activity and healing processes [32].

4.3. Leukocytes Increase Factor. In 2009, Dohan Ehrenfest et al. [33] introduced the concept of leukocyte-rich PRP (LR-PRP), characterized by a total white blood cell (WBC) count higher than the WBC level in the native blood, versus leukocyte-poor PRP (LP-PRP), which is characterized by a total WBC count lower than the WBC level in native blood.

The concentration of leukocytes (which contain enzymes such as collagenase) could have a different impact on cartilage and tendon cells. The results of a meta-analysis of randomized trials suggest that LR-PRP may be more effective than LP-PRP for the treatment of tendinopathies [4].

A recent systematic review and meta-analysis of available studies regarding treatment of knee osteoarthritis also indicated that LR-PRP has more proinflammatory properties than LP-PRP [34].

4.4. Dose of Injected Platelets (Concentration (PLTs) × Volume). In 2016, Magalon et al. analyzed 20 PRP preparations and concluded that the dose of injected platelets can vary from 0.21 to 5.43 billion, depending on the device used, meaning that the increased fold between two devices can vary by more than 25-fold, and therefore, it is perfectly understandable that the therapeutic effects may be different [35]. A positive correlation between the platelet dose and the quantity of growth factors delivered at the injections site has been shown in this paper, as well as in previous studies.

4.5. The Global and Relative Composition of the PRP. This refers to the characterization of PRP preparations, by their concentration of PLTs, leukocytes, and red blood cells (RBCs).

One of the most important concerns in PRP products is the detection of the level of RBCs contamination, an aspect that is otherwise not included in the current classifications of PRP. It has been shown that a great number of PRP preparation devices provide more RBCs than PLTs in the final PRP product [36]. The degradation processes of RBCs present in the PRP preparation generate pathophysiological processes including hemolysis and eryptosis, with potential consequences such as inflammation, radical oxygen reactions, cellular stress, vasoconstriction, and impaired cell metabolism, thus impeding the beneficial action of PRP [37].

Furthermore, in sports medicine, an *in vitro* study performed on human synovial cells showed that using PRP rich in erythrocytes and leukocytes promotes synoviocyte cell death and proinflammatory mediator production, which could lead to intra-articular injury [38].

4.6. The Capacity of the Device to Recover All the Platelets from the Blood (the Recovery Rate in Platelets). This parameter refers to the percentage of PLTs captured in the PRP from

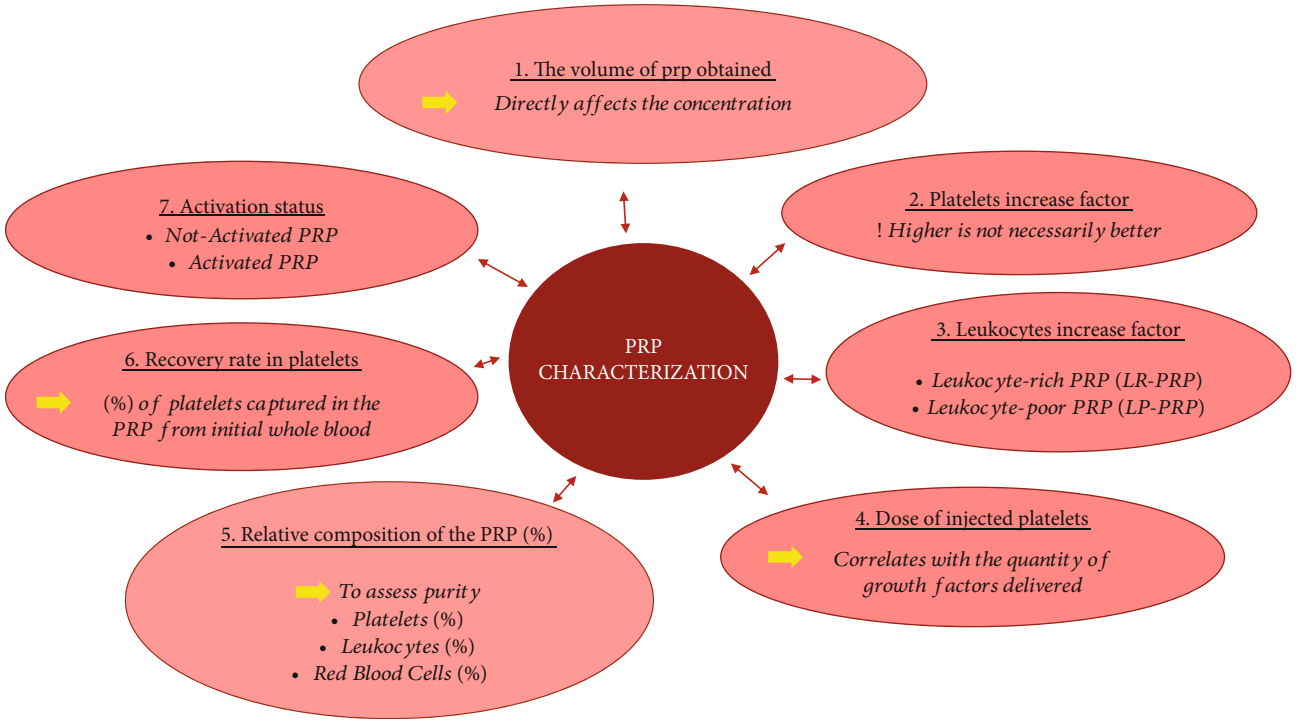

Figure 1: Biological parameters that need to be evaluated for a proper analysis of the platelet-rich plasma (PRP) preparations.

initial whole blood. It is not directly correlated to clinical efficacy, but it is rather an indicator of the performance of the PRP preparation device and is currently used only in DEPA classification [36].

In various studies, the recovery rates in PLTs for several devices ranged from 13.1% [39] to 79.3% [40]. In a recent 2021 technical and biological analysis of authorized medical devices for platelet-rich plasma preparation, Magalon et al. [41] found that these systems still fail to recover approximately 40% of the platelets from the blood during the preparation step (the mean recovery rate in PLTs is approximately 60%). Furthermore, most of the preparations that did manage to achieve a recovery rate higher than 80% also presented a high rate of RBC contamination, highlighting that the available centrifugation cycles are not yet capable of reaching both PRP purity and high recovery rate of PLTs.

4.7. Activation Process. Activation is required for platelets to degranulate and release bioactive molecules [42, 43].

To this regard, before injecting PRP into the target tissue, exogenous platelet activators can be added, such as calcium chloride, thrombin, or collagen. On the other hand, some authors state that PRP products can be used without the addition of an activation agent because platelet activation is spontaneously induced due to exposure to dermal collagen and thrombin once PRP is injected [9, 44].

The issue concerning the need for exogenous activating substance is controversial but is important for clinicians to always specify the activation status since different PRP activation agents can affect the physical form of the final product and might also influence the release curve of growth factors.

5. International Biological Classifications Designed to Define PRP Need to Be Implemented in Clinical Practice

In the late years, a lot of international scientific societies with interest in advancing PRP therapies have issued recommendations to optimize and standardize the use of PRP products, and seven different biological classification systems are currently available to simplify the use of PRP: the Paw Classification system [43], the Mishra classification system [42], PLRA classification [45], DEPA classification [36], MARSPILL classification [46], the ISTH classification [47], and AAOS edited consensus recommendations [48].

These classifications assess different biological parameters and have different thresholds concerning the concentration of PLTs in the whole blood, the global and relative composition (PLTs, leukocytes, and RBCs) of the PRP, cells increased or decreased factors compared to blood, the dose of injected PLTs, and the remaining percentage of PLTs in PRP from initial whole blood (recovery rate in platelets). But most importantly, overall, all these classifications clearly state that to correctly classify PRP, a cell count is implied both for the blood and the PRP samples.

One of the latest recommendations is issued by the Platelet Physiology Subcommittee of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), which highlights the need to take into account the content and the quality control of the platelet preparation to ensure that clear correlation can be established between the biological quality and the clinical outcomes [47].

The consensus recommendations edited by the American Academy of Orthopaedic Surgeons (AAOS) are further providing minimum standards for product development and clinical research evaluating PRP, with no less than 23 parameters that need to be reported in clinical trials, to allow for reproducibility and comparison across studies. The same prestigious scientific society recommended that physicians and institutions offering PRP biologic therapies should establish postmarket monitoring and quality assessments, by using high-quality biorepository-linked registries [48].

Implementation of all these classifications and recommendations is very important, but, unfortunately, they are still not adopted in clinical practice.

This is mainly because in real life practice such systematic biological characterization is expensive and time consuming. It requires access to an automatic cell counter or a collaborative work with a medical laboratory and access to a performant software that would further allow exploitation of the generated data by qualified staff. Very few physicians manage to achieve this at an individual level, and in the future development of Centers of Excellence in Regenerative Medicine could allow a homogenization of the practices and empower follow-up of international recommendations.

6. Conclusions

Autologous platelet-rich plasma therapy describes a treatment without standardization of manufacturing process and guidelines of use, and thus, the evidence for its efficacy is conflicting and limited in quality. The differences detected in the effectiveness of this biologic therapy may be caused by the wide disparities in PRP preparation and a lack of standardization in blood processing methods. Validation of this therapy will demand further standardization of PRP preparation methods for clinical use, with a focus on the quantitative and qualitative characteristics of the injected PRP.

Conflicts of Interest

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

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Axial and para-axial loading response evaluation on human cadaver-harvested lumbar vertebral blocks: *In vitro* experiment with possible clinical implications for clinical practice

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Abstract. The aim of the present study conducted on the lumbar spine was to confirm that the pronounced decrease in resistance in the system is a phenomenon that can be eminently affected by the adaptive changes that occur at the level of the intervertebral disc at axial mechanical stresses. The biomechanical trial was carried out on 11 lumbar segments L1-L5, gathered from adult human cadavers. The dissection considered the complete keeping of all bone, disc, articulated and ligamentous components in their anatomical position. All 11 samples were frozen 24 h prior to the performance of the biomechanical measurement. The specimens were placed in the testing device, their placement being conditioned by the estimated dimensional values. Thus, to calculate the load and axial resistance, the models were placed vertically, central between the test machine ferries. The testing was carried out by applying variable forces and displacement supervision. The displacement interval was represented by a segment of 0-10 mm with surveillance every 2 mm. Mobility in the sagittal plane (flexion earlier in our case) was much higher than that in the frontal plane, obviously limiting mobility via the intervertebral disc and articular complex through the presence of arches. Statistical analysis demonstrated the lack of any correlation values between the two types of movements (R^2=0.005507), underlining the absence of any prediction elements. A noteworthy aspect is that the correlations appeared low, statistically insignificant, even within the same movement in the sagittal plane between the two levels, L1-L3 and L3-L5 (R^2=0.610427), which may lead to the possibility of the emergence of significant differences in mobility between respective levels. The behavior type of the monitored specimens and the results obtained allowed the mapping of objective parallelism between the values obtained and the behavior *in vivo* of the lumbar vertebral segment.

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Key words: lumbar spine, mechanical stresses, vertebral blocks, axial load, eccentric load

Introduction

Experimental dynamics conducted on the lumbar spine aims to prove that, given that the vertebral bodies are rigid systems, the pronounced decrease in resistances in the system is a phenomenon that can be eminently affected by the adaptive changes that occur at the level of the intervertebral disc at axial mechanical stresses. Moreover, these considerations are applicable to the disc where degenerative processes have occurred (1,2). However, it does not perfect the ways of distributing loads and demands that occur in the vertebral body and the intervertebral disc. Such a model, associated with the biodynamic axial load study, has the advantage of providing relevant information on bone movements and the changes in soft neighborhood structures. This approach should not be neglected in specific pathology management of the area (1). The behavior of the monitored specimens, especially the results, allows for objective parallelism between the values obtained in the present study and the lumbar vertebral segments *in vivo* behavior.

Materials and methods

The biomechanical trial included 11 lumbar segments L1-L5, gathered from adult human cadavers. To obtain various anatomical preparations with biomechanical characteristics as close to those, *in vivo*, specimens were obtained from fresh, non-formalin-preserved human cadavers, preserved by freezing at -22°; after sampling, the anatomical preparations were maintained at temperatures below freezing. The decision to protect the samples only by freezing was taken after

examining the specialists' studies from the literature and which confirmed, with arguments, that this represented the most effective preservation method concerning the mechanical strength and elasticity of the intervertebral disc for maintenance in saline solution, which decreases disc resistance (3). After the isolation, the adjacent muscularity was removed from the preparations to view the osteoligamentous spine fully. The dissection considered the complete keeping of all bone, disc, articulated and ligamentous elements in their anatomical position to maintain the mechanical characteristics specific to the region as close as possible to the physiological conditions. Preparations were frozen 24 h prior to the performance of the biomechanical measurement (3).

The test device included the following. i) Tensile strength-compression universal test machine, with the capacity of 200 kN, type LBG 200, with a rigid construction in 2 columns, for bending, compression, and tensile strength static tests, with an accuracy that observes the standards of ISO 7500-1, precision class 0.5 and minimal resolution 0.80 microns. The device has transmission channels of high resolution and synchronized data, with high precision power cells, with a piston displacement transducer with double direction. ii) Command system and digital control with software module through which the machine operation is performed, setting of work parameters occurs, and reading the results specific to the bending/compressing/tensile tests is carried out. The system ensures the real-time follow-up of test parameters: force, displacement, elongation and allows the printing of results and test diagrams, achieved using a digital regulator for force, displacement, deformation with closed-loop control, and data acquisition. iii) The programmable package on Windows platform; a programmable package for statistical tests or according to the operator needs, represented by TC SOFT application software (Microsoft Corp.).

Each vertebral segment under test was comprised of five vertebrae and four lumbar intervertebral discs prepared according to the previous description. The specimens were placed in the testing device, their position being conditioned by the estimated dimensional values. Thus, to calculate the load and axial resistance, the samples were placed vertically, central between the test machine ferries.

The testing was carried out by applying variable forces and supervision. The displacement interval was represented by the segment 0-10 mm with maintenance every 2 mm. For each displacement interval, the force values were recorded, at the initial moment and the end of displacement, and the 'return' resistances encountered after 2, 4, 6 and 8 min, with the registration of forces at those moments. The force values (expressed in Nm) reflected the behavior of the assembly vertebrae-discs-ligaments. To differentially quantify the resistances from the column of bodies and those induced in the system by the arches column, separate testing occurred at compression, control samples, represented by ligamentous-disc-vertebral blocks (2 lumbar vertebrae and the corresponding disc) from which all the posterior arch elements were removed, mainly the zygapophyseal complex (Fig. 1).

The lateral positioning (eccentric placement) (Fig. 2) of preparation allowed the eccentric force application; thus, the flexion/extension movement could be simulated. The metric displacement monitoring followed the consistent application of a 5 Nm equal force, quantified displacement in turn in angular values, which was expressed in degrees.

Results and Discussion

Axial loading study revealed the existence of three types of behavior concerning the lumbar segment at compression, namely:

Type I behavior at the axial loading represented the most uniform behavior type. As observed from the recorded data, the lumbar vertebral block showed a fast and pronounced adaptation after 2 min, an increase of 30-70% of the initial values, decreasing gradually up to final values.

By the evolution model of system forces, this type of behavior is deemed optimal for intense and sudden moments and loads. At the same time, however, the decreased intensity of response in 4-8 min suggests the efficiency of such a system on time intervals of relatively low duration.

Type II was characterized by an approximately constant interval of resistances within 2-4 min. This type of behavior suggests the existence of an interval in which the resistance at axial loads remains relatively constant for a more extended period, a period in which the changes in the intervertebral disc are minimal. Type II represents the type of system able to sustain the intense loads (with absolute superior values to those from type I) for more extended periods without suffering notable distortions.

Type III represented the type of 'intermediary' or 'compromise' behavior, in which the interval of uniform resistances is the most extensive. Thus, after a substantial reduction between 0 and 2 min, a relatively uniform interval appears between 2 and 6 min, after which the disc resistance actually 'collapses' or is markedly reduced up to the end (Fig. 3).

Type III presents the lowest values of resistance in the final stages (min 8) for all displacement intervals, except for the intervals of 0-2 min. Such behavior suggests the possibility of developing some effective resistances at the axial external loads on longer intervals. However, when these resistances are exceeded, the disc-vertebra assembly can no longer face the loads.

Regarding the distribution of the three types within the tested batch, the overwhelming percentage was represented by type III, i.e., by the most adjustable type to loads, with 55% of the cases. It was followed, in order, by type I (27%) and type II (18%).

Table I and Fig. 4 summarize the type of behavior of the three types suggested in terms of the forces [Newton-meters (Nm)] related to the displacement (mm), a linear model behavior similar to those provided by literature (4).

Thus, type I constantly presents the lowest resistances, displacement of 10 mm, and type II involves the most potent displacement forces (i.e., resistances). By contrast, type III reconfirms the position of the intermediate kind with the uniform behavior. An exciting aspect of the study was represented by the comparative analysis of how the three lumbar vertebral types behaved in the five displacement moments: 2, 4, 6, 8, and subsequently 10 mm. Thus, at a displacement of 2 mm, type I presents the lowest values and, at the same time, it 'concedes' resistance at the fastest rate, the type II resists to the highest loads, but on a relatively short interval, and type III

Figure 1. Vertebra with posterior arch elements removed.

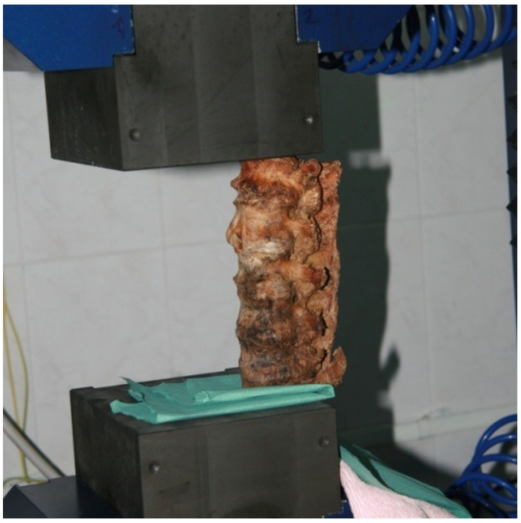

Figure 2. Lateral positioning of the vertebral segment.

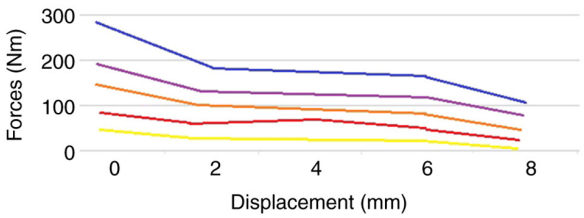

Figure 3. Axial loading type III behavior. Yellow, 2 min; red, 4 min; orange, 6 min; purple, 8 min; blue, 10 min.

is constantly placed in an intermediate position, both in terms of values and in terms of dynamics. In addition, in the case of the 2 mm displacement, the highest value differences were recorded between the three suggested types (Fig. 5).

In the case of the 4 mm displacement, type I maintains the behavior model, descending steeply after min 2; type II loses the interval between min 2 and 4 but, at the same time, is reduced less while type III not only constantly maintains the trend but also manifests a slight peak at min 4. At the same

Table I. Three types of axial loading behavior.

Displacement (mm)	2	4	6	8	10
Type 1	52	82	122	177	257
Type 2	68	91	144	211	246
Type 3	61	88	136	184	255

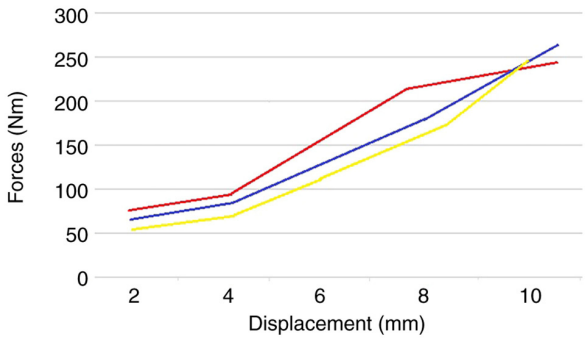

Figure 4. Forces/displacement. Yellow, type I; red, type II.

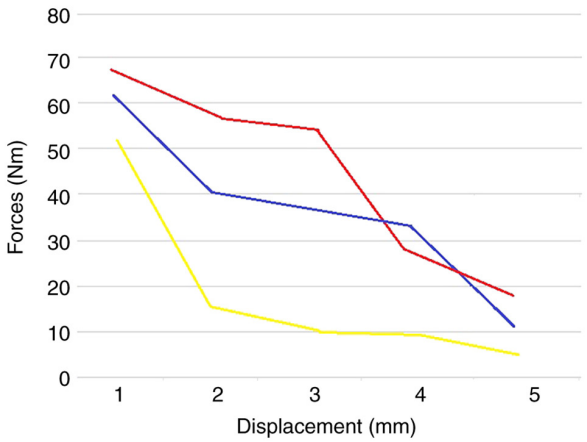

Figure 5. The 2-mm displacement. Yellow, type I; red, type II, and blue, type III.

time, the resistance of this type is decreased significantly after min 6, so that, at the end of the experiment, it presents the lowest responsiveness (Fig. 6).

After compression of 6 mm, the behavior of the three models was maintained, with two exceptions: The value difference between them was significantly low, and the interval peak disappeared from min 4 of type III. As in the previous case, at the end of the load, the resistance of type III was found to be the lowest (Fig. 7).

As the displacement interval increased (8 and 10 mm), the value differences of resistances between the three types was reduced while the evolving trend remained. Moreover, type III resistance decreased below the one of type I before minute eight (Fig. 8).

This phenomenon was even more apparent at the 10-mm displacement when the resistance of type III was the lowest after only 3 min. Thus, at higher displacements, type III loses effectiveness. In reality, such a displacement is specifically

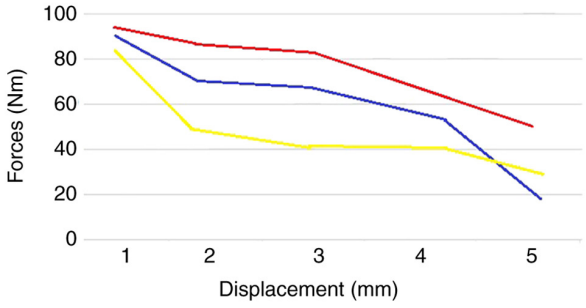

Figure 6. The 4-mm displacement. Yellow, type I; red, type II, and blue, type III.

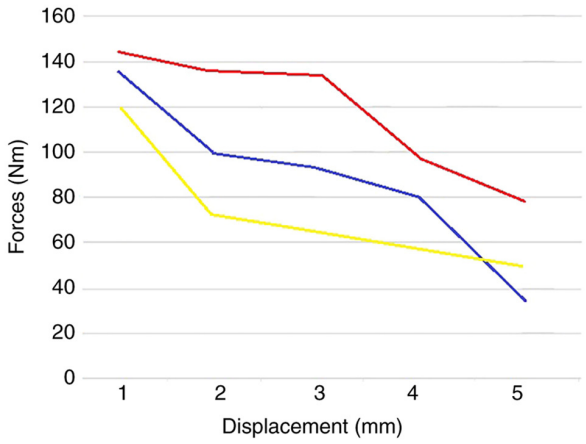

Figure 7. The 6-mm displacement. Yellow, type I; red, type II, and blue, type III.

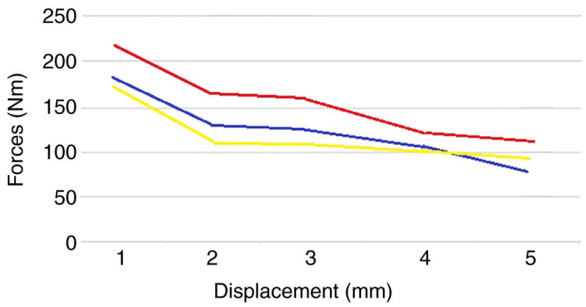

Figure 8. The 8-mm displacement. Yellow, type I; red, type II, and blue, type III.

only examined *in vitro*, while *in vivo*, such amplitudes are impossible in the case of a simple axial load, more evident in complex applications, composed and, very often, exceed physiological limits (Fig. 9).

All the above considerations support that: type I is the type of adequate response to prolonged and average to low-intensity loads; type II, responds to maximum loads, but for relatively reduced intervals; while type III is indeed the type with the uniform behavior, at least in the load margin and physiological displacements.

Eccentric loading was focused on the reproduction of the characteristic movements of flexion in the sagittal and frontal plane. The eccentric placing of the specimens allowed the bodies' axial loading to reach the edge of the column, followed by the corresponding 'pinching' of the discs in the relevant plane and correlation distances with angular values.

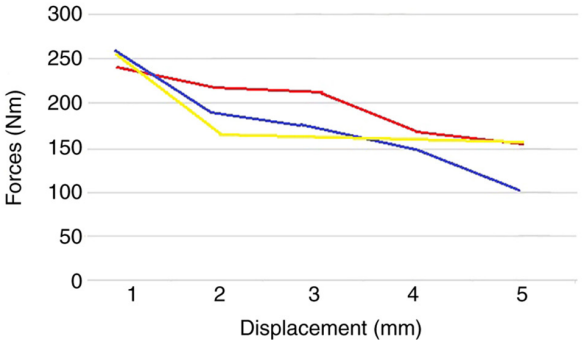

Figure 9. The 10-mm displacement. Yellow, type I; red, type II, and blue, type III.

The values obtained (Table II) are comparable to those offered by the existing literature (5), relative to the loads imposed.

It is noteworthy that the mobility in the sagittal plane (flexion earlier in our case) is much higher than that in the frontal plane, clearly indicating limited mobility by the intervertebral disc and articular complex by the presence of arches. Statistical analysis demonstrated the lack of any correlation values between the two types of movements (R^2=0.005507), underlining the absence of any elements of prediction. An interesting aspect is that correlations appeared low, statistically insignificant, even within the same movement in the sagittal plane between the two levels L1-L3 and L3-L5 (R^2=0.610427), suggesting the possibility of the emergence of significant differences in mobility between respective levels. The only values perfectly correlated were evident in the case of lateral flexion between the two analysis levels (R^2=0.938386), which suggests an element of uniformity in this type of mobility. It is an aspect worthy of considering in the analysis of phase III discopathy etiopathogeny clinically.

The calculation of loads and resistances in the vertebral-disc system has always been a concern for many authors, who employed various calculation and testing methods (6). As absolute values, in an orthostatic position, a weight of 47 kg presses on L4-L5 disc; with any change in the position due to muscle tension, this weight is converted into a load intervertebral disc pulpous nucleus between 282 and 726 kg. The longer the levers and the heavier the weight to lift, the higher the loads on the pulpous nucleus, which may reach up to 1,200 kg. In order to increase the accuracy of the determinations, center probes were placed at the level of the intervertebral discs to record intra-disc pressure. Experiments have shown that, on the third lumbar disc, on a 70 kg individual, each disc carries, in dorsal decubitus position, a pressure of 21 kg, in lateral decubitus carries 70 kg, sitting position carries 100 kg, with trunk reclined forward at 45˚ carries 150 kg, and in sitting position with the trunk reclined forward at 45˚ holding a weight of 20 kg pressure of 210 kg (6).

Despite the limitations, the current study on biomechanical resistance and the outcome from investigating the axial lumbar vertebral level, has highlighted several important issues.

Linders and Nuckley were among the first to study the displacement mechanism of the nucleus pulpous substance inside the IVD and found that, in the flexion of the spine, the front of adjoining vertebral plateaus approach and their rear part is separating, and the nuclear substance moves with part

Table II. Eccentric loading values.

Anatomical sample	Sagittal flexion		Frontal flexion	
	L1-L3	L3-L5	L1-L3	L3-L5
1	32.9	20.7	29.7	16.4
2	43.2	24.1	34.5	18.4
3	42.1	21.4	33.4	18.6
4	33.2	20.1	24.6	13.6
5	24.9	18.4	35.4	19.7
6	41.2	29.1	21.5	11.2
7	36.5	24.1	28.7	15.4
8	29.7	19.7	28.4	13.7
9	39.7	20.8	24.3	9.1
10	43.2	22.7	33.5	20.4
11	40.1	20.8	30.1	15.7
Median	36.97273	21.99091	29.46364	15.65455

of the mass (most) towards the rear of the IVD, albeit some of it moves towards the front, while on the right side flexion, most of the nucleus mass moves to the left and a small part of it moves to the right (7). The aforementioned studies are opposed to the hypothesis of the pulpous nucleus as a single mass, moving like a 'ball' inside the IVD.

According to this study, while the vertebral bodies are rigid systems, the pronounced reduction in the resistance system is a phenomenon that can be placed exclusively on adaptive changes that occur in the intervertebral disc. Resistance-pronounced decrease in the system within minutes is nothing but a volumetric adaptation to mechanical axial loads of the intervertebral disc. Decreased mobility in the system increases stress on the structures, while disc elasticity prevents this phenomenon. In addition, such considerations are applicable in the case of the disc at which the degenerative processes occurred (4,8,9). At present, it is certain that the resistance of the disc varies depending on the degree of degeneration, leading, in turn, to a decreased resistance in cases of moderate degeneration and increased rigidity, and subsequently to a decrease of the force absorption power, in case of severe degeneration (6,7,10-19). Furthermore, the parallelism between the load on the one hand, and the disc degeneration, on the other hand, can engage the fibrous annulus in a vicious cycle, which invariably results in irreversible ruptures (7).

Another aspect worth mentioning is that, while the preservation of preparations tried, as much as possible, to limit the biochemical changes that occur *in vitro*, the experiment was conducted at ambient temperature and not the average body temperature, which, in turn, may alter the values obtained.

In the current study, type III, the type considered most adaptable, represented the majority (55%), i.e., more than double each of the other two types. It was followed by type I, the one that, after a swift adjustment to the initial moment, 'conceded' resistance in a uniform manner.

In conclusion, the behavior type of the monitored specimens and especially the results obtained allowed the mapping of objective parallelism between values found in the current study and behavior *in vivo* of the lumbar vertebral segment. A critical aspect revealing the degree of objectivity of the study is that this type of behavior manifested throughout the test interval of 10 mm, an element confirming that preparations behaved uniformly, a biomechanical behavior induced obviously by the morphological substrate. Additionally, monitoring the behavior of the lumbar complex for long intervals of time after application of forces is an original element that allows the evaluator to determine as objectively as possible, concerning the evolution of adaptation, the likely degree of disc degeneration. Examination of disc loads and especially the behavior of vertebral segments under various load types and values can contribute on the one hand to identifying the potential etiologies of pathological manifestations at this level and, on the other hand, to the development of effective prevention and/or treatment strategies in the matter. Thus, correlating the disc behavior and the load makes biomechanics, besides a prognostic factor, a genuine therapeutic factor in disc regeneration.

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Availability of data and materials

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Authors' contributions

DMI, CI, IB, PB, EG and MGI conceived and designed the study. DMI, PB, FV, SIM, MGI and BO acquired the data. DMI, PB, IB and MGI assessed the authenticity of the data. CI, IB, EG, FV and SIM analyzed the data. DMI, PB, IB, MGI and BO validated the results. EG, MGI, DMI, PB, FV, CI and IB were responsible for the preparation of the original draft. SIM, EG, FV and BO, were responsible for the final manuscript editing. DMI, PB, CI, IB, SIM and MGI supervised the manuscript publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Benefits of crenotherapy in digestive tract pathology (Review)

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Abstract. Balneotherapy, a branch of physical and rehabilitation medicine using the natural factors of balneal resorts for therapeutical purposes to modulate the symptoms of numerous diseases, represents a non-pharmaceutical therapeutic alternative, easily accepted by patients and used both preventively and curatively. Crenotherapy, a branch of balneotherapy, is the method in which mineral waters are used as a therapeutic internal cure by ingestion. This procedure is performed in spa resorts (where these natural resources exist), and the ingestion of mineral water takes place at the source (spring), in the quantities recommended by the medical rehabilitation physician, according to specific regimens for the condition to be treated. Depending on their physical and chemical composition, the therapeutic mineral waters fall into several categories, having clear indications for certain pathologies. Hypotonic, isotonic, or slightly hypertonic mineral waters are recommended in diseases of the digestive tract and hepatobiliary conditions. Over time, studies have been conducted to determine the effect of these types of treatments, highlighting the complex influence of crenotherapy on the gastrointestinal tract, with favorable results, therefore the use of mineral water intake in various pathologies being recommended. The current review focuses on the existing literature data and refers to the main progress made in understanding the benefit, indications, and crenotherapy procedures in the management of gastrointestinal disorders.

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Key words: mineral waters, crenotherapy, digestive tract diseases, alkaline, oligoelements, ulcer

Contents

1. Introduction

As therapeutic tools, mineral waters are most frequently used as internal cure (crenotherapy) and also in the external cure, using various individualized techniques based on the type and stage of the disease or based on the patient's response and co-morbidities (1).

In Antiquity, on the Dacian territories, the Geto-Dacian population founded settlements in the vicinity of the natural springs (Utidava, Petrodava), which were used for therapeutic purposes, upon the indications of the priests. There are documents attesting that 2500 years ago, Herodotus recommended the 21-day cure of mineral water, a fact scientifically confirmed only in the twentieth century (2).

Over time, many digestive pathologies have been referred to obtain the beneficial effect of crenotherapy; even the term and the beneficial link were later defined. The impact on the digestion pathways, on the peristalsis, or the potential antiseptic effect of some mineral waters raised the interest for improving different pathological situations (3). Physicians are already trying to add their possible effects to current pharmacologic or surgical treatments, considering that balneal treatments can

provide a noninvasive way that can improve the quality of life in many cases (4).

In 1924, in Bucharest, A. Teoharia was the first researcher preoccupied with the physicochemical properties of mineral waters and their benefits on human health. This research was later published in 1929 in Somes Archive by the writer Virgil Sotropa, which presents the popularity of these natural resources in different pathologies, including gastritis and bile or liver diseases (5). During the second half of the twientieth century, the therapeutic effects of mineral waters of Romania were scientifically confirmed, some of them being recommended for use as crenotherapy of digestive and hepatobiliary tract diseases (6).

Most countries benefitting from natural springs of mineral waters have undertaken research in terms of the physicochemical composition and also on the effects of mineral waters, identifying the uses of various types of mineral water for specific pathologies. In 2009, a centralized classification of mineral waters was performed, according to European legislation (1). Thus, the main categories are bicarbonate-rich, sulphurous, chloride, high-calcium, high-magnesium, fluoridated, and ferruginous (chalybeate) mineral waters (1,7).

Mineral waters, based on biological activity, can be classified as: cathartic waters, diuretic waters and waters with antiphlogistic properties (8).

This article reviews the clinical studies conducted in the last five years on the effect of mineral waters in gastrointestinal disorders, using data from the MEDSCAPE and PubMed portals; 9 eligible studies were identified (Table I).

2. Pathogenic background for crenotherapy usage

There are certain chronic diseases of the digestive and hepatobiliary tract, for which spa treatment, including crenotherapy with mineral waters, can contribute to a better result, by complementing the effects of basic dietary, pharmacological and surgical therapies. The mineral waters used in the internal cure represent, in fact, a non-pharmacological therapy, considering the natural, albeit pharmacological resource, based on their chemical content.

Thus, depending on their composition, there are indications of therapeutic cures in which simple alkaline or bicarbonate waters are used. These contain at least 1 g of salts/liter, with the predominance of bicarbonate ion bound to Na and K cations. The effects of these waters on the digestive tract reside in the action of Na/K bicarbonate, an alkaline substance, confirmed by studies carried out by specialists from spas and the National Institute for Rehabilitation, Physical Medicine, and Balneology (1,5,9). The ingestion of these waters reduces the chlorhidropeptic secretion (when ingested an hour and a half before a meal) or stimulates it (administered during a meal), also affecting gastric motility and bile ducts, such as fluidization of the bile, depending on the method of administration. In Romania we provide this treatments in Slanic Moldova and Sangeorz Bai balneary resorts (1,6,9).

Another category, alkaline-earth sodium bicarbonate, high-calcium, and high-magnesium waters have an excitation effect on gastric secretion (Calimanesti-Caciulata, Slanic Moldova) through the predominance of CO_2, NaCl, H_2S, or sulfates (1,5).

Sulfurous waters (Baile Olanesti, Calimanesti-Caciulata, Mangalia, Herculane) stimulate gastric secretion, are choleretic, cholecystokinetic, gastric, and intestinal motor stimuli. Hydrogen sulfide regulates the function of biological systems and plays a vital role in various systems and diseases (9).

The hydrogen sulfide present in these waters is responsible for the stimulating effect on the enzymatic and metabolic processes in the gastrointestinal mucosa, stimulating the chemoreceptors, a fact that has been experimentally confirmed (1,7,9-11). Depending on the chemical composition of different sulfur waters, their effect on the digestive tract is different, as follows: poorly mineralized sulfur waters (Mangalia, Baile Olanesti springs 10 and 24) stimulate gastric secretion initially, a stimulation followed by an inhibition phase; those from Caciulata spring 1 (one) and Calimanesti spring Pausa 1 and 2 have a stimulating effect on the gastric secretion, those from Calimanesti spring 1 stimulate secretion after an initial phase of inhibition, and those from Baile Olanesti springs 5, 7 and 12 inhibit secretion (1).

Oligoelements play essential roles in the metabolism and function of the gastrointestinal and renal tract (12). In sodium, magnesium, and calcium sulfate waters, the effects are choleretic, cholecystokinetic and laxative (Amara, Baltatesti, Nicolina-Iasi). Mineral calcium and magnesium sulfate waters are confirmed to have ahypoglycemic and lipid-lowering action. They may be used as alternative therapeutic approaches of metabolic syndrome and mild forms of diabetes mellitus, preventing progression to disabling complications, such as diabetic retinopathy of diabetic foot (13,14). The effects on the secretion of the stomach are different, depending on the complexity of the chemical composition: the water from Amara decreases gastric secretion. At the same time, that of Bizusa spring 1 intensely increases the secretion and acidity of gastric juice (1,5).

Chlorosodium waters used as internal treatment are hypotonic or isotonic waters, with concentrations below 10 g Na Cl/liter. These stimulate gastric and intestinal secretion, activating digestive enzymes (pancreatic-intestinal amylase), increasing gastrointestinal peristalsis reflexively, the elements present in these waters stimulating the vagus nerve (1,6,9).

The indications regarding the dosage and the administration method are individualized and depend on the patient's condition and the experience of the physician (5). The choleretic effect is helpful in biliary dyskinesia but must be used with caution in patients with biliary microlithiasis, being a possible trigger for calculous migration and cistic or common bile duct (CBD) obstruction, responsible for acute cholecystitis and angiocholitis, which requires rapid surgical treatment (15,16). The potential harmful effects of sulfate waters may lead to increased transaminases in vulnerable subjects, thus is contraindicated in patients with hepatitis (17). The comprehensive medical history and the complete clinical evaluation of the patient before crenotherapy indication are imperative. The benefits, the potential side effects, and therapeutic alternatives should be considered before its initiation (18).

The integrity and functioning of the gut microbiota can be influenced by infections, medicine/food supplements and preservatives. Hydrogen sulphide, in optimal concentrations,

Table I. Clinical studies conducted in the last five years on the effect of mineral waters in gastrointestinal disorders.

Authors	Country	Year	No. of patients	(Refs.)
Dupont *et al*	France	2014	244	(27)
Bothe *et al*	Slovenia	2015	106	(28)
Naumann *et al*	Germany	2016	100	(29)
Quattrini *et al*	Italy	2017	Not mentioned	(25)
NIH, ClinicalTrials.gov	France	2017	166	(30)
Dupont *et al*	France	2019	226	(31)
Dragomiretska *et al*	Ukraine	2020	90	(32)
Constantino *et al*	Italy	2020	Not mentioned	(33)
Chavez *et al*	Brazil	2020	50	(34)

protects the gut flora from the lesions caused by these stressors, stimulate the resorption of the inflammation and cure local wounds (19,20). The H_2S concentration in healthy adults varies between 0.3-3.4 mmol/l (19), the higher concentrations being able to cause injury to the intestinal microbiome, disturbing the processes in which it is involved (21,22).

In current practice, sulphurous waters with concentration below 20 mg/l are used as an internal cure, because H_2S has anti-diabetic effects, anti-oxidant properties and antiaging effects, as it inhibits the DNA alteration (23,24).

Alkaline water also results in a decrease in cardio-vascular risks, reducing morbidity and mortality in the elderly population presenting comorbidities (25).

The sulphurous mineral waters above this concentration of 20 mg/l are only used as external cures (for instance, Pucioasa waters of 1,152 mg/l). In addition, the quantity of water used in sulphurous water crenotherapy is small, 50-100 ml/day up to a maximum of 400 ml/day (1).

Alkaline water having a minimum of 1 g of salts/liter with a preponderance of the bicarbonate ion and a pH above 7.0, has proven health-promoting benefits, leading to an equalization of the pH of the entirebody (26).

The main diseases of the digestive tract treated by crenotherapy are gastro-duodenal dyspepsia, chronic gastritis, duodenitis, gastric or duodenal ulcer, sequelae after surgery, idiopathic gastric dyspepsia, chronic, nonspecific enterocolopathy, chronic constipation, unidentified digestive disorders due to irrational alimentation and stressful conditions (1,9,17).

Although crenotherapy is widespread, the current literature lacks evidence-based data including any exact classification of the different types of mineral waters that can be used as a general guide for the balneology practitioner, or therapeutic protocols available. There is not yet a defined global consensus regarding the indications, therapeutic programs, and their application; all of these differing from one country to another and from one spa to another in terms of crenotherapy. Currently, no international agreements have been established for this type of therapy (10). Romania remains one of the countries with a great variety of natural therapeutic resources, holding 30% of Europe's supplies. In addition, the richness of spas (160) renders Romania a vital pillar in the development of spa tourism (1,5,6).

3. Evidence-based literature data focused on the benefit of crenotherapy for GI (gastrointestinal) tract pathologies

Our review intended to expose the current evidence-based clinical benefit of crenotherapy in gastrointestinal (GI) diseases by analyzing the research reported between 2015 and 2020 on Medline or PubMed online database.

Low functional transit or functional constipation, one of the most common symptoms related to the GI tract, especially in women, has been an issue of crenotherapy indication. Dupont *et al* demonstrated in a double-blind, randomized, placebo-controlled study on 244 women from France the benefit of crenotherapy with intensely mineralized water rich in magnesium and sulfates in the alleviation of functional constipation during the second week of treatment. The researchers also affirmed a significant decrease in the need for laxative drug use after the same interval (27). Another similar placebo-controlled, double-blind study conducted on 106 patients suffering from functional constipation published by Bothe *et al* evaluated the efficacy and safety of magnesium and sulfate-rich mineral waters on gut function. The results indicated improved intestinal peristalsis and stool consistency, as well as increased quality of life for patients consuming 300-500 ml of mineral water for six weeks (28).

Naumann *et al* published in 2016 'Forshende Komplementarmedizin', a double-blind, randomized, placebo-controlled study on the effects of richly mineralized sulfurous water consumed daily for six weeks, and compared the impact to that of carbonated water consumption in a control group. The efficacy of the treatment was observed after three weeks from the baseline by increasing the intestinal motility in the experimental group (2.02±2.22 bowel movements per week) as compared to the control group (0.88±1.67 bowel movements per week) (29).

In 2017, Quattrini *et al* published an article on the effects of natural mineral waters on health, depending on their physico-chemical characteristics. The study conclusions indicated that bicarbonate mineral water neutralizes gastric acid secretion, increasing the pH of the gastric lumen, stimulating the release of digestive hormones. Chlorinated mineral water stimulates gastric emptying and gastroduodenal peristalsis; the magnesium waters relieve constipation, reducing the associated symptoms. In addition, the functionality of the biliary tract is

improved by complex mineral waters such as sulfurous-bicarbonate-calcium-magnesium-rich water, due to the anions with choleretic and cholagogue function and the high-magnesium waters favor the relaxation of the Oddi sphincter, allowing the bile to drain, thus improving the activity of the biliary tract (25).

Another ongoing interventional clinical trial, initiated by Bourgeois in 2017, published partial results on the prophylactic effect of rich magnesium mineral water over the hypomagnesemia induced by anti-epidermal growth factor rceptor (EGFR) monoclonal antibodies, indicating a decrease in the incidence of hypomagnesemia as a side effect in such patients. The research was performed on 166 patients undergoing treatment with anti-EGFR monoclonal antibodies for different neoplasia (metastatic colorectal cancer or head and neck cancer), associated with ingestion of mineral water rich in magnesium and poor in sulfates. The mineral water used in this research (Rozana-France) has the highest concentration of magnesium (160 mg/liter) and the lowest sulfate content (30).

Later, in 2019, Dupont *et al* published a multicenter, double-blind, randomized, controlled study concerning the immediate effect of crenotherapy with magnesium and sulfurous mineral water in functional constipation, confirming the effectiveness and safety of the mineral water use as a first-line curative procedure. The studied patients consumed 1.5 liters/day of Hepar mineral water (France) for 14 days. Researchers confirmed that the mean duration of treatment to obtain constipation relief was shorter in the Hepar mineral water experimental group than in the control group (6.4 vs. 7.3 days, P>0.05) (31).

In 2020, Dragomiretska *et al* published a study in which 90 patients from Ukraine were divided into three equal arms according to the main treatment: i) pharmacologically with proton pump inhibitor, ii) bicarbonate mineral water, and iii) magnesium sulfur bicarbonate mineral water. The results indicated the highest efficacy on dyspepsia and pain syndrome of treatment applied in the third group (32).

Other literature data referring to the effects of magnesium-sulfur mineral waters on functional constipation concluded that mineral waters such as Hepar (France), Ensinger Schiller Quelle-ESQ (Germany), and Donat Mg (Slovenia) represent a natural option for treatment in functional constipation, having a laxative effect, without noticeable side effects (9,32). The authors recommend the daily magnesium consumption of at least 20 mM for a minimum of one week to obtain the mentioned effects (32).

Another article published by Constantino *et al* in 2020 focused on sulfurous water as a medical resource in certain diseases. The authors concluded that daily ingestion of sulfurous-magnesium mineral water increased gastric secretion and stimulated its evacuation, modulating the motility and releasing the substances accompanying the digesting process (33).

In 2020, a recent study made by Chavez *et al* highlighted the effects of crenotherapy with alkaline water (pH=8.0-10.0) administered for five months for gastritis symptom relief. The results showed that besides the beneficial effect of crenotherapy with alkaline water on gastritis symptoms, an improvement in the RNA expression was present, the alkaline water intake significantly increasing the expression of various genes related to the digestion process (34).

4. Conclusions

Natural mineral waters represent a valuable therapeutic resource in some circumstances, representing an alternative to pharmacological treatment or an adjuvant, relieving the symptoms of gastrointestinal diseases and increasing the quality of life. According to their composition, therapeutic mineral waters are recommended for consumption as an internal cure in both physiological and pathological conditions, allowing a decrease in drug consumption or the reduction of doses used in classical treatment regimens. Further research focusing on the benefit of crenotherapy is expected, literature being insufficient especially in regards to functional and organic digestive diseases.

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Availability of data and materials

All information found in this review is documented by relevant references.

Authors' contributions

AIS, LM, MD and AdPS conceived and designed the review. FV, AnPS and SIM acquired the data. MGI, AnPS and CV analyzed the data. AIS, FV and SIM validated the results. LM, MGI and AdPS were responsible for the preparation of the original draft. AIS, LM, MR and AnPS were responsible for the final manuscript editing. AdPS, LM and CV supervised the manuscript publication. SIM, CV, AIS and FV revised and made all the corrections required for final manuscript publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Brain - Derived Neurotrophic Factor - a Marker for the Balneal Treatment of Chronic Low Back Pain?

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Up till now, to our knowledge, there are no studies evaluating serum Brain - Derived Neurotrophic Factor (BDNF) levels in patients with degenerative chronic low back pain under rehabilitation treatment. BDNF is a neuroprotein associated with neuropathic pain and represents an important mediator of the effects of physical exercise. Complex balneal treatment with hot Techirghiol sapropelic mud reduces pain and increases serum levels of BDNF in these patients.

Key words: degenerative pain, BDNF, balneal, sapropelic mud

The main cause of low back pain (LBP) worldwide is lumbar disc herniation (LDH). LDH, a degenerative disease which induces narrowing of the spinal canal, seems to be associated with several single nucleotide polymorphisms (SNPs). For example, seven SNPs were genotyped in a Chinese study performed over 1072 patients [1] and a relation was found between these SNPs and brain derived neurotrophic factors (BDNFs) and their genes (BDNFOs).

BDNF is part of the neurotrophin family of growth factors. They are related to the canonical nerve growth factor, playing an important role in the maturation and differentiation of neurons. Low levels of BDNF are associated with neurodegenerative disorders as Parkinson's disease, multiple sclerosis or Alzheimer disease [2]. Data in medical literature related to BDNF level and its involvement in LBP is controversial, some studies revealing elevated levels of BDNF after pain-relieving methods of physical therapy [3], some others: high levels of plasma BDNF in old women with LBP compared to pain-free controls [4].

Considering the growing burden of LBP worldwide, the studies over how balneal treatment affects neurotrophic factors involved in neural regeneration and protection after spinal cord injury or peripheral nerve disorders can represent the beginning of a new approach in rehabilitation and non-pharmacological therapies [5, 6]. Under these circumstances, we consider our study over the serum level of BDNF in patients treated for LBP with sapropelic mud from Techirghiol lake to be important and proving that balneal treatment significantly modifies the serum level of BDNF.

Experimental part

We present a prospective case-control cohort study, which included 50 patients hospitalized for 2 weeks in the Balneal and Rehabilitation Sanatorium of Techirghiol (BRST). Patients signed an informed consent and the study was approved by the ethical committee of the Sanatorium. Patients with degenerative chronic LBP, with indications for balneal treatment, both women and men, were included in the study. Exclusion criteria were: any inflammatory diseases, high blood pressure, cardiac failure, any pulmonary, renal, endocrine, neurologic or oncologic diseases, skin lesions, any antidepressant treatments. Patients were divided into two groups: hot mud bath group (HMBG) and a statistically matched control group (CG). Patients in the first group benefited from hot mud baths treatment and complex rehabilitation treatment such as electrotherapy, kinetotherapy and massage therapy. The control group had the same treatment, except for the hot mud baths. Each patient was clinically tested before and after treatment. Schober index, finger ground distance (IDS) index (for evaluation of lumbar spine mobility) and the visual analogue scale (VAS) for evaluation of pain were monitored. For each patient blood samples were collected in the beginning and in the end of treatment in order to determine the BDNF serum levels For quantitative detection of BDNF we used a sandwich high sensitivity Eliza kit: Human BDNF PicoKine form Booster Biologic Technology (USA) and Eliza reader StatFax 4700 Microstrip Reader Awareness Technology (USA) Blood prelevation was performed in the same conditions for every patient and laboratory testing was performed by the same doctor. Patients completed a demographic questionnaire regarding age, gender, residence, personal history of pain, body mass index (BMI), frequency of treatment in BRST (twice a year, as indicated, once a year, sporadically and for the first time). Hot mud bath therapy involved diluting 10-15 kg of sapropelic mud, from Techirghiol Lake, in a water tub. The patient was immersed in the hot mud bath for 20 minutes, at 38-39^{0}C under supervision of a physiotherapist.

Statistical evaluation of obtained data was performed using Wilcoxon test (level of significance: 0.05) for dependent samples, the nonparametric Mann-Whithney U test (level of significance: 0.05) for independent samples. Chi-Square test (with $p < \alpha = 0.05$ level of significance) and Spearman's rho were also used. Minimum, maximal, median and Interquartile Range values were obtained and compared.

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Results and discussions

Most of our patients were women, the median age, in both groups, was 54 years old and the majority of the patients included in the study were overweight and had urban residence.

The demographic features of our groups are detailed in Table 1.

We evaluated VAS scores at admission and discharge for each patient and we discovered significant lower VAS values at discharge than VAS values at admission. (Figure 1).

The Wilcoxon test confirmed statistically significant differences of VAS median values before and after treatment for CG ($p<0.001$) and for HMBG ($p<0.0001$), (Table 2).

The result of Wilcoxon test for Schober test values in HMBG patients confirmed statistically significant differences between the median values at admission and those at discharge $p<0.001$ (Table 3). Analyzing the *finger –ground index* for both groups at admission and discharge, we did not find any statistically significant differences (Table 3).

We evaluated BDNF serum levels for each patient at admission and at discharge (Table 4).

According to the non-parametric Mann-Whithney U test there were no significant differences between serum BDNF values of the two groups at admission ($p=0.123 > 0.05$) while at discharge the values significantly differed between groups ($p<0.001$) (Figure 3). In the same time the Wilcoxon test confirmed that within each group the values of serum BDNF at discharge were significantly different from the ones at admission ($p< 0.001$) (Figure 3).

According to Box-Plot representation (Figure 3) the BDNF values in control group were higher at admission than at discharge, while in HMBG the BDNF values were higher at discharge than at admission. We did not find any correlation between BDNF serum values and regular (once or twice per year) or sporadic balneal treatment. We did not discover any significant correlation of serum BDNF

		Hot Mud Bath Group	Control Group
Number		25	25
Age (years)		54.00±9.147 (39-68)	54.00±6.813 (41-67)
Gender	Male	7	10
	Female	18	15
BMI (Kg/m²)	18.50-24.99	9	15
	25-29.99	8	5
	30-34.99	5	2
	35-39.99	2	3
	≥40	1	0
Urban Residence		88% (22)	92% (23)
Frequency of balneal treatment:	biannual	12%	8%
	annual	48%	24%
	occasional	20%	32%
	First time	20%	36%
VAS score at admission		7.08±1.63	5.28±1.99
Quantified Schober index at admission		4.76±0.72	4.68±0.90

BMI=body mass index, VAS=visual analogue scale

Table 1
DEMOGRAPHIC FEATURES OF BOTH GROUPS

		Lot	
		CG	HMBG
VAS at admission	Minimum	2.00	5.00
	Maximum	9.00	10.00
	Median	5.00	7.00
	Percentile 25	4.00	6.00
	Percentile 75	7.00	8.00
	Mean	5.28	7.08
	Standard Deviation	1.99	1.63
VAS at discharge	Minimum	2.00	2.00
	Maximum	8.00	8.00
	Median	3.00	4.00
	Percentile 25	3.00	3.00
	Percentile 75	4.00	5.00
	Mean	3.96	4.32
	Standard Deviation	2.11	1.68

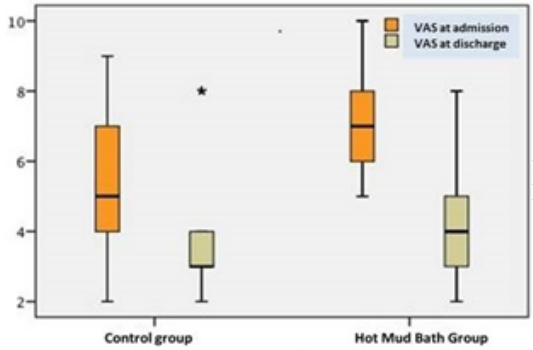


Fig. 1. VAS scores distribution for patients from the study groups and Box-Plot representation of VAS scores at admission/ discharge for each of the studied groups.

Group				VAS at admission	VAS at discharge
Spearman's rho	Control group	VAS at admission	Correlation Coefficient	1.000	.571**
			Sig. (2-tailed)	.	.003
			N	25	25
		VAS at discharge	Correlation Coefficient	.571**	1.000
			Sig. (2-tailed)	.003	.
			N	25	25
	HMBG	VAS at admission	Correlation Coefficient	1.000	.823**
			Sig. (2-tailed)	.	.000
			N	25	25
		VAS at discharge	Correlation Coefficient	.823**	1.000
			Sig. (2-tailed)	.000	.
			N	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

Table 2
SIGNIFICANCE OF VAS VARIATIONS

Table 3

SPEARMAN'S RHO. SIGNIFICANCE OF SCHOBER'S TEST AND *FINGER-GROUND INDEX* VARIATIONS

			Schober at admission	Schober at discharge			"Finger – ground index" at admission	"Finger – ground index" at discharge
Control Group	Schober at admission	Correlation Coefficient	1.000	.787**	"Finger – ground index" at admission	Correlation Coefficient	1.000	.999
		Sig. (2-tailed)	.	.000		Sig. (2-tailed)	.	.000
		N	25	25		N	25	25
	Schober at discharge	Correlation Coefficient	.787**	1.000	"Finger – ground index" at discharge	Correlation Coefficient	.999**	1.000
		Sig. (2-tailed)	.000	.		Sig. (2-tailed)	.000	.
		N	25	25		N	25	25
Hot Mud Bath Group	Schober at admission	Correlation Coefficient	1.000	.526**	"Finger – ground index" at admission	Correlation Coefficient	1.000	.958**
		Sig. (2-tailed)	.	.007		Sig. (2-tailed)	.	.000
		N	25	25		N	25	25
	Schober at discharge	Correlation Coefficient	.526**	1.000	"Finger – ground index" at discharge	Correlation Coefficient	.958**	1.000
		Sig. (2-tailed)	.007	.		Sig. (2-tailed)	.000	.
		N	25	25		N	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4

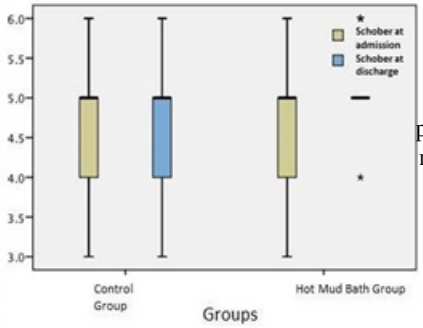
LEVELS OF SERUM BDNF IN CONTROL GROUP AND HOT MUD BATH GROUP

	Group			
	Control Group		HMBG	
	BNDF at admission (pg/mL)	BDNF at discharge (pg	BNDF at admission (pg/mL)	BDNF at discharge (pg/mL)
Minimum	318.90	39.50	346.00	1016.80
Maximum	1842.00	1698.00	1649.20	1998.00
Median	1416.00	498.70	1211.40	1646.70
Percentile 25	690.00	272.20	1051.00	1402.40
Percentile 75	1771.00	986.40	1304.00	1846.50
Mean	1257.56	654.44	1147.56	1629.97
Standard Deviatic	528.23	504.77	316.67	266.69

with gender or age, with the exception of CG where the older the patient the lower the BDNF at discharge ($p<0.001$) (Table 5).

Chronic LBP represents a major health problem [7-9] and diverse treatments in order to reduce pain and disability are experimented [10]. BDNF, a neuroprotein associated

		Group	
		Control group	HMBG
Schober at admission	Minimum	3.00	3.00
	Maximum	6.00	6.00
	Median	5.00	5.00
	Percentile 25	4.00	4.00
	Percentile 75	5.00	5.00
	Mean	4.68	4.76
	Standard Deviation	.90	.72
Schober at discharge	Minimum	3.00	4.00
	Maximum	6.00	6.00
	Median	5.00	5.00
	Percentile 25	4.00	5.00
	Percentile 75	5.00	5.00
	Mean	4.72	5.12
	Standard Deviation	1.02	.44



Fi. 2. Schober index distribution for patients from the study groups and Box-Plot representation of Schober index quantified scores at admission/discharge for each of the studied groups.

	HMBG	CG	Mann-Whithney U test
Median BDNF at admission (pg/mL)	1211.40 (IQR: 253)	1416.00 (IQR: 1081)	p=0.123 (p>0.05)
Median BDNF at discharge (pg/mL)	1016.80 (IQR: 444)	498.70 (IQR: 714.2)	P<0.001
Wilcoxon test	P<0.001	P<0.001	

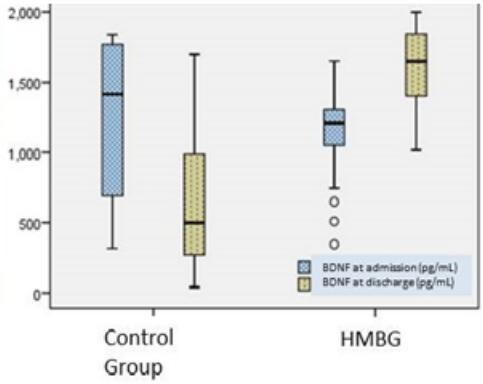


Fig. 3. Statistical evaluation for serum BDNF within each group and between groups both at admission and at discharge and Blox Plot representation of BDNF values of each group at admission and at discharge

HMBG			BDNF at discharge pg/ml	Patient's age
Spearman's r	BDNF at discharge pg/	Correlation Coefficient	1.000	-.012
		Sig. (2-tailed)	.	.953
		N	25	25
	Age	Correlation Coefficient	-.012	1.000
		Sig. (2-tailed)	.953	.
		N	25	25
Control Group			BDNF at discharge pg/ml	Patient's age
Spearman's r	BDNF at discharge pg/	Correlation Coefficient	1.000	-.657**
		Sig. (2-tailed)	.	.000
		N	25	25
	Age	Correlation Coefficient	-.657**	1.000
		Sig. (2-tailed)	.000	.
		N	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5
AGE CORRELATION WITH BDNF AT DISCHARGE IS SIGNIFICANT ONLY IN CG

with neuropathic pain and mediator of the effects of physical exercise [11, 12], has been extensively studied in recent years, especially regarding the influence of exercise on chronic LBP [13]. The patients in our study had a complex treatment (including hot mud baths) for chronic LBP and we searched if serum levels of BDNF are influenced by this kind of treatment.

Overweight and obesity are reported as risk factors for chronic LBP [6, 9] and analyzing the features of our patients we discovered that less than half of our patients had a normal weight. Obesity itself was found to associate with low levels of BDNF especially in patients with mutations of the gene encoding its receptor - tyrosine kinase receptor type 2 (Ntrk2) [14]. This situation was described especially in children with obesity and psychomotor retardation, as in Biddle-Bardet syndrome [14, 15]. But, despite our expectations, we did not find any significant correlation between BDNF and BMI. This comes in concordance with a similar meta-analysis performed by Sandrini L and colab. in 2018 [16]. We did not find any correlation between serum levels of BDNF and the periodicity of balneal treatment, either.

As women were the majority of our patients, we take into account a future extension of our study, considering the relation between balneal treatment, the levels of serum BDNF and gynecological pathology. A study from Wessels J.M.et al. identified prominent BDNF and Ntrk2 isoforms in the human uterine muscle and endometrium [17]. As magnesium administration induces an increase in BDNF level [17] but also inhibits uterine muscle contraction [18] a possible relation can be found between the two mechanisms involved in uterine relaxation, with possible therapeutic consequences. Another possible future question could be, in this context, if pain decrease could be related also on uterine BDNF-calcium effect, superposed on the known calcium actions on the myometrium [19, 20].

Endometriosis, a benign disease represented by existence of endometrial tissue outside the uterine cavity, is associated with important abdominal pain [21.], sometimes mistaken for LBP. A recent study [22] found that BDNF concentrations in serum and peritoneal fluid were significantly high in women with endometriosis with pain, suggesting that BDNF can play a role in pain's origin. Furthermore, women with endometriosis use physiotherapy and kinesiology in order to reduce pain [23].

VAS evaluation for both groups revealed statistically significant reduction of this parameter and this confirms

that rehabilitation treatment reduces pain [24, 25]. The possible explanation for the greater reduction of VAS score in CG than in HMBG after treatment results from the immediate short term pro-inflammatory effect induced by balneal treatment with sapropelic mud, inflammation that cease in several days from the balneal treatment. So, VAS score is expected to diminish after several days, also. Unfortunately, we did not have the possibility to reassess VAS score in patients from HMBG after discharge. Regarding Schober test we found statistically significant differences only for the patients from the HMBG. This demonstrates the improvement of flexibility of the lumbar spine segment after balneal treatment with hot sapropelic mud, as other studies have revealed [25].

We found that serum BDNF levels are significantly and reversely correlated with patients' age only in CG: the higher the age the lower the BDNF. As our groups did not differ significantly regarding age, perhaps this reduction is induced by balneal treatment without sapropelic mud administration. The result can be biased by the small number of patients included in the study. Statistically significant differences for serum levels of BDNF in both groups, at discharge, were found. Our results revealed a significant reduction in BDNF levels in CG and a statistically significant augmentation of BDNF levels in the HMBG patients. We do not have a clear explanation for the reduction of BDNF levels in CG, we can just suppose that the physical effort during kinetotherapy, even if aerobic, was not strong enough to induce a rise in BDNF level. We compared the results in our CG to other two studies in medical literature. One revealed that only high-intensity locomotor exercise increased the levels of serum BDNF compared to moderate intensity physical exercise in patients with incomplete spinal cord injuries who are not carriers of Val66Met single-nucleotide polymorphism [26] and in another one, in a meta-analysis over 29 studies regarding the effect of exercise training on resting levels of BDNF in peripheral blood, Dinoff A et al. found that aerobic but not resistance training increased blood BDNF levels [27]. In the meantime, the reduction in BDNF serum level in our CG comes in opposition with the results of a study in which aquatic physical therapy twice per week for 5 weeks increased the level of BDNF [3]. In another study, [4] the use of analgesic or antidepressant drugs induced a significant reduction of serum BDNF in old women after an acute episode of LBP. Extrapolating, we can consider that balneal therapy, without sapropelic mud, may have the same effect over serum BDNF levels. We did not find any medical data to compare with the increased levels of serum BDNF in our patients who received balneal treatment with sapropelic mud.

Conclusions

In our study, balneal therapy with Techirghiol sapropelic mud induced a significant elevation of serum BDNF levels, associated with significant pain reduction according to VAS score, and with a significant improvement in lumbar mobility as Schober's test revealed. As we far as we know, up to this moment, there are no studies regarding BDNF serum levels in patients with degenerative chronic LBP under mud therapies, so we think that our study brings significant information in this field and it can represent the starting point for other similar studies over a bigger number of patients.

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EFFECT OF TECHIRGHIOL SPECIFIC CLIMATE FACTORS ON THE PATIENTS QUALITY OF LIFE WITH DEGENERATIVE LUMBAR PAIN

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Abstract. The Balneal and Rehabilitation Sanatorium of Techirghiol benefits from a multitude of natural factors such as the salted water of the lake, the sapropelic mud, the marine climate of the region; the lake Techirghiol, near the Black Sea, is a former lagoon and the complete separation between the lake and the sea occurred relatively recent. The most common pathology treated in the Sanatorium is the locomotor pathology followed by the neurologic pathology. Regarding the localisation of the pain, the lumbar pain is by far the most frequent, followed by knee and cervical pain. The salty water and the sapropelic mud of the lake Techirghiol have been the subject of numerous research studies. The aim of present study is to evaluate whether Techirghiol specific climatic factors influence the quality of life patients with degenerative lumbar pain under specific balneal treatment. We evaluated 25 patients, aged between 30 and 65 years, with chronic low back pain, hospitalised for rehabilitation treatment in Balneal and Rehabilitation Sanatorium of Techirghiol for a period of 2 weeks. The patients were treated with cold mud baths on the Techirghiol lake shore. All patients were evaluated using the analog visual scale and lumbar disability questionnaires before and after the treatment. The climatic factors such as air temperature, water temperature and humidity were recorded daily during the treatment. Climatic factors among the effects of balneal cures influence the pain and the quality of life of patients with low back pain. Techirghiol specific climate along with the specific balneal treatment of the Techirghiol Lake, such as salty water and sapropelic mud provide a significant improvement of the quality of life of patients with degenerative lumbar pain.

Keywords: balneal, Black Sea, Techirghiol, research.

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AIMS AND BACKGROUND

Within the last years, balneal therapy became an important therapy and hence the need for a scientific research into the benefits of the so-called thermal medicine. Until now, there is no research into the extent to which the climate factors of the balneal resort have an effect on the treated patients. It is known that degenerative low back pain is very common upon the active and the elderly population and is successfully benefiting from a good response to balneal treatments[1–3].

Therapeutic spas baths and resorts offer a good atmosphere of health and physical movement and also provide relaxation and stress relief. Mud therapy is intensively studied over the last recent years because of its multiple properties and because patients can do the therapy throughout the entire year in the balneal resorts. During the summer time, in the Balneal and Rehabilitation Sanatorium of Techirghiol (BRST) the mud therapy is applied as cold therapy also, at the Techirghiol lake shore[4–6].

The Balneal and Rehabilitation Sanatorium of Techirghiol benefits from a multitude of natural factors such as the salted water of the lake, the sapropelic mud, the marine climate of the region; Techirghiol Lake, near the Black Sea, is a former lagoon and the complete separation between the lake and the sea occurred relatively recent. The climate of the area is temperate continental, steppe, with marine influences due to the geographical location of the resort. This type of climate leads to reduced thermal comfort, which implies an intense adaptation of the body, especially through its thermoregulation mechanisms. The water of the lake is strongly hypertonic, and has a concentration of about 80 g of mineral salt per liter and a total mineralisation of 52 g/l. Being so concentrated, the water can only be used in external cure as cold or warm baths in the pool or bath. The water exerts its therapeutic effect through its temperature, its chemical composition and its high density which results in an unloading of body weight at immersion in water[7].

Peloidotherapy is an area of convergence between conventional medicine and alternative practices/complementary medicine, among high-specialised and holistic medicine and the special climate of the Techirghiol lake appears to inhibit the inflammation mediators[4–6].

The most common pathology treated in the Sanatorium is the locomotor pathology followed by the neurologic pathology. Regarding the localisation of the pain, the lumbar pain is by far the most frequent, followed by knee and cervical pain[6].

Chronic low back pain is a major problem nowadays. Up to 84% of the general population experiences occurred an episode of low back pain throughout life[7]. It is the fifth most common reason for a visit to a physician and the third most common reason for a physical impairment in people aged 45–64 years. Mechanical disorders are the cause in about 90% of cases. Most episodes of low back pain resolve quickly and are not incapacitating, however, the cases of chronic low back pain occur most of the treatment challenges and healthcare costs[8,9].

The aim of our study is to evaluate whether Techirghiol specific climatic factors influence[10] the quality of life patients with degenerative lumbar pain under specific balneal treatment. The quality of life was analysed with Roland Morris, Oswestry and Quebec lumbar disability questionnaires[9,11].

EXPERIMENTAL

The study group had a total of 25 patients who signed consent where they have been provided all information about the participating research and have been assured confidentiality, in compliance with the inclusion and exclusion criteria. We present a prospective clinical study conducted in BRST of Romania. The patients were admitted in August 2016 for a period of 2 weeks. Inclusion criteria were: patients with degenerative low back pain, with correct indication of thermal cure, both women and men, hospitalised in BRST. Exclusion criteria were any of the situations mentioned as contraindications of thermal cure, such as: presence of inflammatory events, cardiac decompensation, high blood pressure, skin lesions, and respiratory, endocrine, neurologic, oncologic diseases. The treatment of the hospitalised patients in BRST consists of peloidotherapy – cold mud baths and adjuvant procedures such as: electrotherapy, kinetotherapy, massage therapy. The cold mud baths were at the shore of the Techirghiol Lake. Subjects assessment included: general clinical examination, completing a demographic questionnaire (age, gender, residence, education level, personal history of degenerative disease, body mass index – BMI), completing the Roland Morris, Quebec and Oswestry questionnaires at admission and discharge. The patients in the group performed daily application with cold mud which is a contrasting therapy. The application of therapy consists of progressive general heliotherapy, application of mud followed by immersion into the lake. The patients had 3 electric procedures per day, one regional massage therapy session daily and kinetotherapy one session per day.

Patients were evaluated at admission and at the end of the cure using clinical evaluation regarding also the painful symptoms; in this case we used the Visual Analogue scale (VAS) for pain (in which 0 represented no pain and 10 severe pain), and they had to complete three questionnaires regarding lumbar disability before and after the treatment. The climatic factors such as air temperature, water temperature and humidity were recorded daily during the treatment. All values were reported as the mean ± standard deviation, where appropriate, as the median. We used nonparametric tests (Wilcoxon Test) for dependent samples.

RESULTS AND DISCUSSION

We evaluated the VAS scores at the admission and discharge for each patient in the tested group and the score ranged at admission (VAS1) between 2 and 9 with a median of 7, and at discharge (VAS 2) the scores were between 0 and 7, with a

median of 4. The Wilcoxon test confirms that there are statistically significant differences of the median values before and after the treatment ($p < 0.001$) (Fig. 1).

Statistics

		VAS1	VAS2
N	Valid	25	25
Mean		5.88	4.08
Median		7.00	4.00
Mode		7[a]	4
Range		7	7
Minimum		2	0
Maximum		9	7
Percent	25	4.00	3.00
	50	7.00	4.00
	75	8.00	5.00

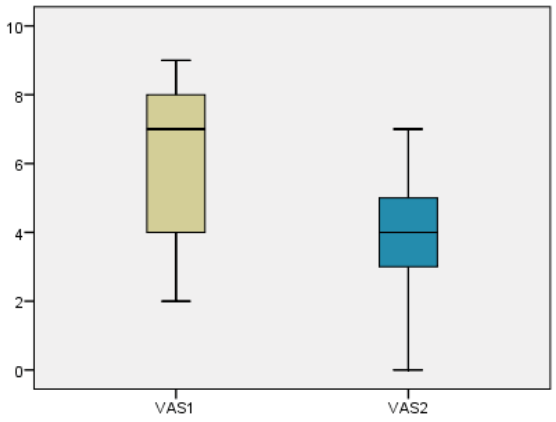

Fig. 1. VAS score evaluation before and after the treatment

The Roland Morris (RM) questionnaire, assessed before (RM1) and after the treatment, (RM2) showed significant differences as well. At admission, patients had scores between 1 and 16 with a median of 9, while at discharge they presented scores between 1 and 13 with a median of 5. The test confirms there are statistically significant differences of the median values before and after the treatment ($p < 0.001$) (Fig. 2).

Statistics

		RM1	RM2
N	Valid	25	25
Mean		8.88	5.60
Median		9.00	5.00
Mode		13	3
Range		15	12
Minimum		1	1
Maximum		16	13
Percent	25	5.50	3.00
	50	9.00	5.00
	75	13.00	8.50

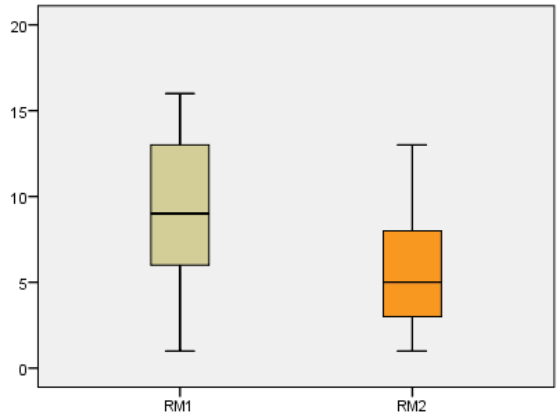

Fig. 2. Roland Morris questionnaire scores before and after the cold mud therapy

Regarding the Quebec (QB) questionnaire, we discovered statistically significant differences between the 2 values, such as: before the treatment (QB1) the scores were between 20 and 58, with a median score of 36, and after the treatment (QB2)

the scores were between 19 and 45, with a median score of 27, which confirms once again significand differences between the median scores ($p < 0.001$) (Fig. 3).

Statistics			
		QB1	QB2
N	Valid	25	25
Mean		35.84	28.16
Median		36.00	27.00
Mode		20	20
Range		38	26
Minimum		20	19
Maximum		58	45
Percent	25	23.50	20.00
	50	36.00	27.00
	75	45.00	33.00

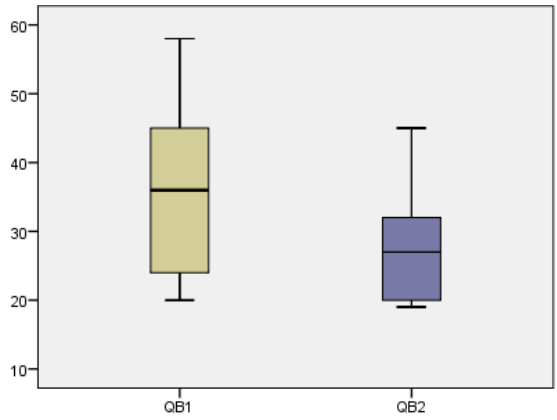

Fig. 3. Quebec questionnaire scores before and after treatment

Analysing the Oswestry questionnaire, the scores before the treatment (OSW1) were between 2 and 40, with a median value of 24, and the scores after the treatment (OSW2) were between 0 and 32, with a median value of 18, which confirms once again significand differences between the median scores ($p < 0.001$) (Fig. 4).

Statistics			
		OSW1	OSW2
N	Valid	25	25
Mean		22.48	16.24
Median		24.00	18.00
Mode		24	12
Range		38	32
Minimum		2	0
Maximum		40	32
Percent	25	16.00	9.00
	50	24.00	18.00
	75	28.00	23.00

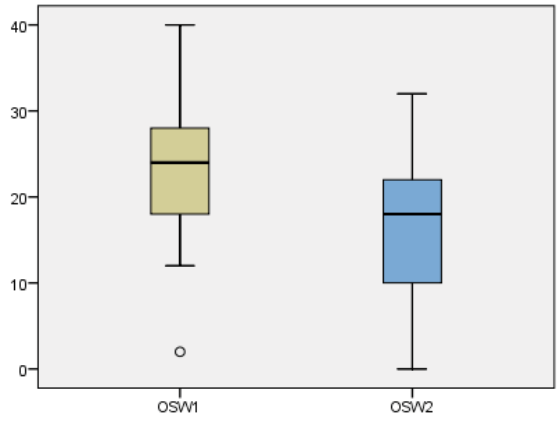

Fig. 4. Oswestry questionnaire scores before and after treatment

Over the 2 weeks in which the patients followed the treatment, the air temperature was between 20 and 30°C, the lake temperature was between 24 and 26°C and the humidity was between 29 and 90% (Fig. 5).

Statistics

		Air temperature (^{0}C)	Water temperature (^{o}C)	Humidity (%)
N	Valid	26	26	26
Mean		26.38	24.88	67.38
Median		26.50	25.00	72.50
Std. Deviation		3.125	0.588	17.137
Minimum		20	24	29
Maximum		30	26	90
Percent	25	24.00	24.75	62.50
	50	26.50	25.00	72.50
	75	29.25	25.00	79.00

Fig. 5. Values of climate factors of the Techirghiol area

According to the graphical exposure of the values of the temperature, even though regarding the temperature of the air were differences of up 10^{o}C during the time the patients performed the balneal treatment, the temperature of the water lake remains between 24 and 26^{o}C. This is an important characteristic of Techirghiol lake.

We tried to find the profile of the patient that responds best to cold mud baths, correlating the age, gender, residence, education level, body mass index with VAS index and with the scores of the lumbar disability questionnaires of the patients with degenerative low back pain, but there were no statistically significant differences.

CONCLUSIONS

Our research suggested that low back pain, evaluated with VAS index, decreased in intensity using cold mud therapy, subjectively appreciated by patients ($p < 0.001$), which brings strong evidence for the clinical effectiveness of balneal treatment.

Regarding the clinical and functional assessment of effectiveness of cold balneal therapy, we evaluated the quality of life of the patients according to the lumbar disability questionnaire scores. We obtained the following results: for Roland Morris questionnaire a decrease statistically significant ($p < 0.001$), for Quebec questionnaire a decrease statistically significant ($p < 0.001$), and also for Oswestry questionnaire a decrease statistically significant ($p < 0.001$). This brings a significant improvement in the quality of life of patients with degenerative lumbar pain after completing 2 weeks of treatment.

The air temperature, the water temperature and the humidity during the time the patients performed the balneal treatment are compliant with the literature data for Techirghiol Lake.

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STATISTICAL VIEW THROUGH BALNEAL ACTIVITY IN TECHIRGHIOL MEDICAL AREA

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Abstract. The lake Techirghiol represents an ancient golf of the Black Sea, with concentrated salted water with good properties for natural treatments. The Balneal and Rehabilitation Sanatorium of Techirghiol (BRST) gained its fame over the years, due to the great number of patients treated here with natural cure factors – salted water of the lake and sapropelic mud extracted from the lake, associated with marine climatic characteristics in a combined heliomarin and thalassotherapy cures. In BRST are treated patients with a wide range of diseases, most of them with osteoarticular and neurological pathology, both adults and children. The aims of the study are: analysis of epidemiological data (gender, age, somatic features), in order to establish the characteristics of the population that benefits from treatment with natural specific factors; to analyse the types of pathology treated in the sanatorium; to determine the addressability of the patients for balneal treatments; to contribute to a common background for research in this field. The study was performed during two years, between May and April, in Balneal and Rehabilitation Sanatorium from Techirghiol. 6281 patients were examined during this study. The patients were admitted for a period of 12 days up to 30 days and they received complex rehabilitation treatment: hydro-kinetic-therapy in the salted water of the pool, alternated with warm mud baths or hot mud wrapping, or cold mud ointment and then swim in the lake, completed with massage, electrotherapy and kinesiotherapy. All patients underwent an initial clinical examination and then the physician filled up a questionnaire, which includes personal data, information about the disease requiring admission, if the patient has in the medical history any balneal treatment and what were the results, and finally the group of affections to which fit the existing symptoms. Data from the questionnaires were statistically processed and plotted. The most frequent reason for admission is by far pain of different causes (96%) and only a small number of patients addressed for a functional deficit. The great majority of patients included in the study presented as main symptom lumbar pain, followed by knee pain and cervical pain. In conclusions, balneal treatment in marine climatic field with salted water and sapropelic mud results in alleviation of pain in most of the patients, also for an important part of patients contribute to improvement of life quality. We hope that in the future more patients will address to this modern balneal centre, due to beneficial effects of sapropelic mud, demonstrated by studies performed by the research centre within sanatorium.

Keywords: balneal, Black Sea, Techirghiol, research.

* For correspondence.

AIMS AND BACKGROUND

Balneal and Rehabilitation Sanatorium of Techirghiol (BRST) is situated on the shore of Techirghiol Lake, near the Black Sea and was established over one century ago. The sanatorium gained its fame over the years, due to the great number of Romanian and foreign patients treated here with natural cure factors – salted water of the lake and sapropelic mud extracted from the lake. Most of the patients are admitted in the sanatorium through state medical insurance system, whereas only a small number come by direct payment. In Balneal and Rehabilitation Sanatorium from Techirghiol are treated patients with a wide range of diseases[1–3], using hot mud and salted water from the lake. Patients are also often using mud as cold mud ointment and then swim in the lake, method known from ancient times as Egyptian method.

Aims of the study were: analysis of the epidemiological data (gender, age, somatic features), in order to assess the characteristics of the population that benefits from the treatment with natural specific factors; to analyse the types of pathology treated in the sanatorium; to determine the addressability of the patients for balneal treatments; to contribute to a common background for research in this field[4,5].

EXPERIMENTAL

The study was performed on 6281 patients, during two years, between May and April, in Techirghiol Balneal and Rehabilitation Sanatorium. The patients were admitted for a period of 12 to 30 days and they received complex rehabilitation treatment: hydro-kinetic-therapy in the salted water of the pool, alternated with warm mud baths or hot mud wrapping, or cold mud ointment and then swimming in the lake, completed with massage, electrotherapy, kinesiotherapy. All patients underwent an initial clinical examination and then the physician filled up a questionnaire, which includes personal data (gender, age, profession, place of residence, weight, height, being smoker or nonsmoker, associated diseases, values of blood pressure and heart beat at admission, stress level), information about the disease requiring admission (predominant symptom, main symptom location, physical activity at home, person who recommended balneal cure), if the patient has in the medical history any balneal treatment and what were the results, and finally the group of affections to which fit the existing symptoms. Data from the questionnaires were statistically processed and plotted. The used questionnaire was proposed by a group of physicians from the sanatorium (Fig. 1).

Balneal treatment center: ***Balneal and Rehabilitation Sanatorium Techirghiol***

Type of therapeutic factors climate
water
mud

Type of cures external
internal
During cure: 11, 14, 18, 21 days

Name ..... Age .....
Surname ..... Sex: M/F.....
Address-No. tel. ..... Profession .....
(City, villag ..... In activity .. Retired ...
Weight, ... Height ..... BMI = m (kg) / (h^2) (m) ..... B.P ..... H.B. ..... Smoking:
No \ Yes (N° cigarettes /day) ..... Diabetes Type ..... Other comorbidities .....

Physical activity performed with coordination \ without coordination, daily, for 2-3 days, weekly, monthly, no physical activity.

Specify the *level of stress* experienced; On a scale from 0-10.....

Clinical Data: Physician *who recommended* the cure: General Doctor .....
Specialist Doctor .....
Non-medical person (friend, relative, etc.).....

The symptom or the health condition that made him to follow the balneal cure
- Pain - cervical, dorsal, lumbar, scapulo-humeral joint, sciatica, shoulder, elbow, fist, hand, hip, knee, ankle, foot, polyarthralgias
- Functional deficit - upper limb, lower limb, upper limb + lower limb, both inferior members, the four members
-Walk - individual - without support or with support - unipodal (cane, crutch, tripod), bipodal (cane, crutches, frame); wheelchairs; immobilized
- Other

Balneal treatment before: first cure, a cure prior ... days, ... months ahead, more than two cures longer than 10 days; every ... months.

Benefits of previous cures: reducing physical pain, reduce drug use, improve life quality, no lasting effect

Groups of pathology (diagnosis)
1. Musculoskeletal conditions: osteoarthritis, particular diseases (tendonitis, fibromyalgia), rheumatoid arthritis, ankilosing spondylitis (other spodyloarthropathy), the traumatic status, other orthopedic sequelae
2. O.R.L.
3. Diseases of the respiratory tract
4. Dermatological conditions
5. Cardiovascular / venous conditions
6. Digestive conditions
7. Endocrine and metabolic disorders
8. Renal and urinary disorders
9. Genital disorders
10. Neurological disorders
11. Psychiatric disorders
12. Pediatric diseases (under 16)

Fig. 1. Questionnaire

RESULTS AND DISCUSSION

Due to the large amount of data, we assess that this study will reveal the most significant results from statistical point of view.

The demographic distribution showed increased interest in balneal treatment for urban population, probably based on the intense and stressful life within large cities (Fig. 2).

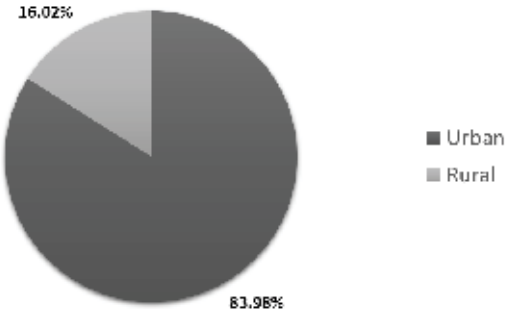

Fig. 2. Demographic distribution

The study reveals low balneal addressability of patients less than 40 years old, increasing progressively with age until 70, with a peak in group of age 50–59 (Table 1).

Table 1. Distribution of the patients upon age

Age	Patients	%
Less than 30 years old	146	2
30–39 years old	396	6
40–49 years old	961	15
50–59 years old	1951	31
60–69 years old	1791	29
over 70 years old	1036	17
Total	6281	100

Statistical analysis revealed that 59% of treated patients were females, whereas only 41% are males (Table 2). We assume that this is due to the fact that women are more actively involved in socio-economical life in recent decades.

Table 2. Distribution of patients upon gender

Gender	Patients	%
F	3714	59.13
M	2567	40.86
Total	6281	100.00

The majority of patients hospitalised in BRST are retired, followed by employees. BRST has two sections: a balneal section, where patients are hospitalised with packages of medical services of 18 days full settled in by 'retirement home'

and a section of hospitalised patients with 12 days packages of medical services, were both retired and employees support a co-payment for treatment. In both sections the number of retired patients prevails (Table 3).

Table 3. Fields of activity

Activity	Patients	%
Employees	2675	42.6
Retired	3334	53.1
Unemployed	9	0.1
No activity	263	4.2
Total	6281	100

Due to the fact that patients addressability peak is between 50–70 years old and most of them are retired with several associated comorbidities, non-smoking patients prevail. In groups, smokers and nonsmokers, most of them are females (Fig. 3).

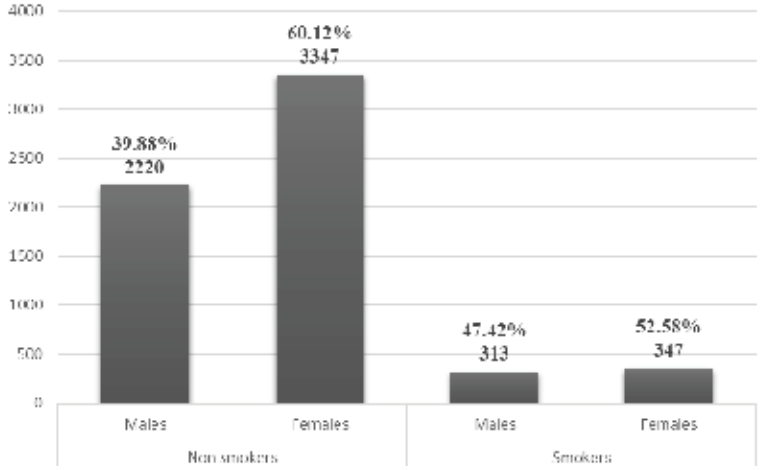

Fig. 3. Prevalence smokers/nonsmokers gender related

The evaluation of the 'Body Mass Index' is presented in Fig. 4 and Table 4. In correlation with the excess weight in the entire population of Romania, overweight patients represent the majority of the studied batch (BMI 25–30 and 30–40), followed by patients with normal weight (BMI 20–25).

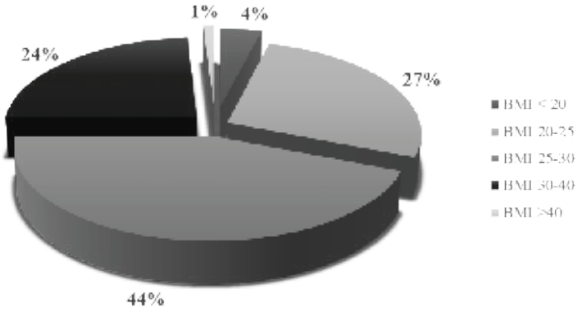

Fig. 4. Body mass index

Table 4. Body mass index

Mean	27.38
Max	64.41
Min	14.06
Standard deviation	4.61
Variance	21.21
Confidence level (P)	0.72
Significance threshold (p)	0.28
Total No. of patients (BMI)	6236
Total	6281

The evaluation of stress on a scale of 0–10 revealed that within the patients requiring hospitalisation, the level of stress is mostly average and above average (Table 5).

Table 5. Stress evaluation

Stress level	Patients
Between 0–2	459
Between 3–4	897
Between 5–6	1875
Between 7–8	2353
Between 9–10	651
Total	6235

The great majority of patients presented as main symptom lumbar pain (mostly degenerative or slipped disc hernia without neurological signs), followed by knee pain (osteoarthritis) and cervical pain (spondylosis or slipped disc hernia).

We noticed that the most frequent affected region is vertebral column (with all segments), followed by knee and hip. Comparing distribution of main symptom in men and women, there is an increased incidence in women of pain as reason for admission, meanwhile in case of functional deficit men are predominant (Fig. 5).

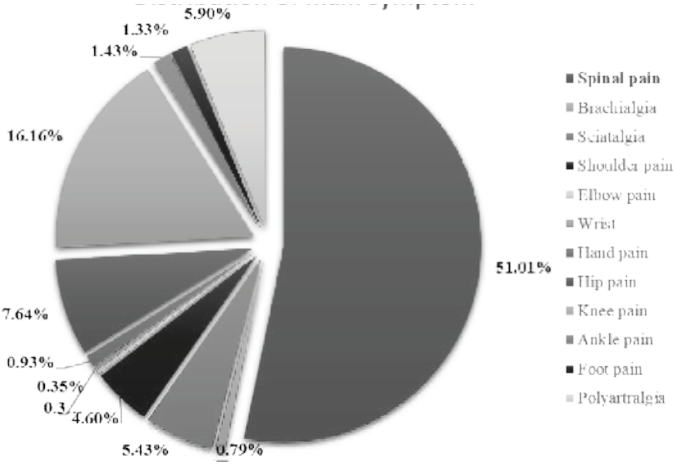

Fig. 5. Gender distribution of main symptoms

Pain is by far the most frequent reason for admission of different causes (96%) and only a small number of patients addressed for a functional deficit (Fig. 6).

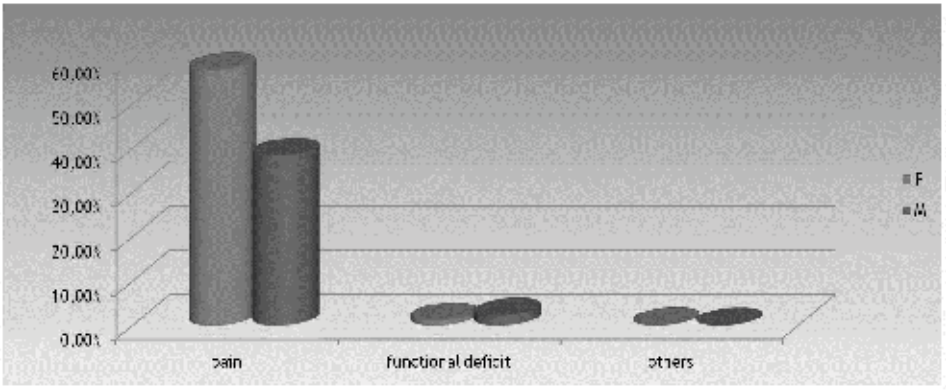

Fig. 6. Distribution of pain

By far, the most frequent pathology in admitted patients is locomotor pathology (more than 90%), followed by neurologic pathology, that includes sciatalgia and brachyalgia, as results of slipped disc hernia (Fig. 7).

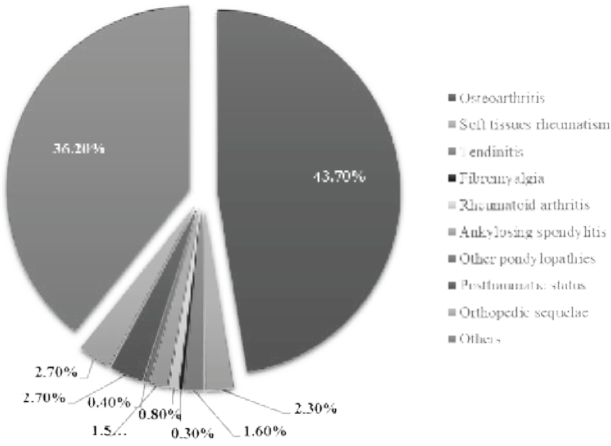

Fig. 7. Pathology frequency

Osteoarthritis with different locations has the greatest incidence, followed by others, in which the most prevalent was lumbar slipped disc hernia without neurologic signs (Fig. 8).

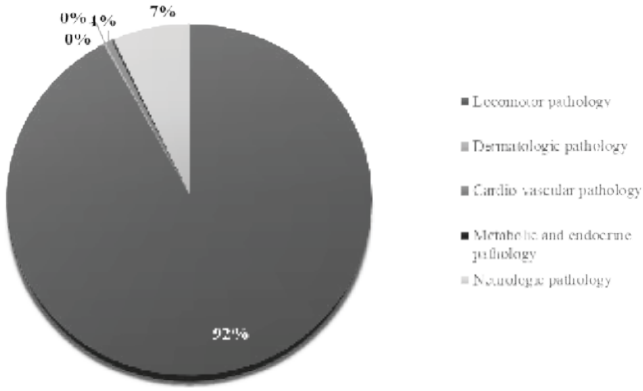

Fig. 8. Prevalence of diagnostics

After the balneal treatment, most of the patients confirmed a decrease of pain, in some cases associated with improvement of life quality. The benefits of the balneal treatment are presented in Fig. 9.

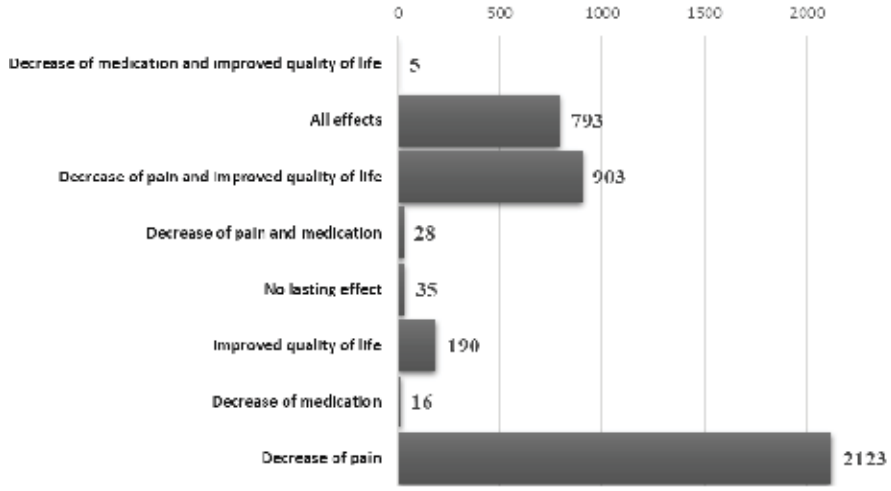

Fig. 9. Benefits of balneal treatment

Judging by the frequency of their visits, the study revealed that half of the patients return every year or two times per year and the other half is for the first time in our sanatorium, probably attracted by its therapeutic fame (Table 6).

Table 6. Patient level of fidelity by balneal treatment

Addressability	Patients	%
First time	3104	49
Two times per year	731	12
Every year	1023	16
More than two times per year	1423	23
Total	6281	100

CONCLUSIONS

Balneal treatment with salted water and sapropelic mud results in alleviation of pain in most of the patients, while for an important part of patients contribute to improvement of life quality.

Actual statistical analysis shows a great addressability of patients from all over the country, most of them with chronic degenerative rheumatism. As the frequency of this pathology is increasing continuously and drug treatment has many side effects, patients are looking for less harmful alternative treatment.

We hope that in the future more patients will address to this modern balneal centre, due to beneficial effects of the sapropelic mud, demonstrated by studies performed within the research centre of the Sanatorium[6].

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The influence of low back pain on health – related quality of life and the impact of balneal treatment

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Abstract

Introduction. Low back pain has a direct and proportional impact on function and a general one on the quality of life. The present study aims to evaluate the functional impact of low back pain using specific self-assessment tools as indexes of appreciation and epidemiological correlations of potential risk factors involved. The conceptual model of our research is based on the importance of correlating symptoms with clinical assessment, using scales of pain, disability, quality of life, and determination of epidemiological correlations of these areas and the determined factors of the pathology.
Material and method. The study group is made up of 106 cases with clinical diagnostic of low back pain, admitted from 28 September 2020 to 28 March 2021, at Balneal and Rehabilitation Sanatorium of Techirghiol. After performing anamnesis, general clinical examination, specific neuro-musculo-skeletal examination, the patients filled the surveys highlighting the impact of their low back pain on functionality and disability deriving from it. The survey included the Oswestry Disability Index, the Functional Independence Measure (FIM) instrument and the Visual analog scale (VAS) score evaluated at the moment of hospitalization and at discharge. Statistical analysis of data was carried out and correlations between variables resulting from study were highlighted. The study was conducted according to the norms of deontology and medical ethics. The authors declare no conflict of interest.
Results and discussions. Lumbar pathology is common in patients who are hospitalized for a complex balneary-physical-kinetic treatment at Balneal and Rehabilitation Sanatorium of Techirghiol. About 80% of patients who have addressed to our unit in which the study was conducted, have presented low back pain. The majority of patients were females, representing 57,55% of the total number. Regarding the patients' age, 58,5% of them were in the 50-70 years interval. The study reveals a major positive impact of our treatment on spinal symptomatology, an effect pointed out by the relevant statistical differences between the admittance and discharge VAS scores($p<0.001$). Reporting the investigated disability with the Oswestry questionnaire of painful lumbar syndrome, and functional evaluation scale (FIM) demonstrates the impact of this pathology on the patient's social life, once again emphasizing the special attention to be paid to axial pathology, both as curative treatment and the importance of prophylactic treatment. Statistical analysis of identified risk factors, reveals the importance of prophylaxis and patient's education in this area. A strong and important statistical correlation was found between the Oswestry total score and the walking and standing items, and a moderate, but strong correlation with the other items. Regarding the sex life item, the correlation is existent, but at a modest level.
Conclusions. The study reveals the importance of correlation of the data obtained from anamnesis, the general clinical examination and the specific examination neuromioarthrokinetic with assessment tools that determine the level of functional independence, the functional impact on social life in high-frequency pathologies treated in medical facilities that provide healthcare in the field of medical recovery. It is necessary to quantify the therapeutic results obtained, in order to assess the level of improvement in quality of life..

Keywords: *low back pain, balneal, functional indicators, quality of life,*

INTRODUCTION

Low back pain is a very common symptom. It occurs in high-income, middle-income, and low-income countries and all age groups from children to the elderly population. Globally, years lived with disability caused by low back pain increased by 54% between 1990 and 2015, mainly because of population increase and ageing, with the biggest increase seen in low-income and middle-income countries (1-3). Low back pain is now the leading cause of disability worldwide.

Low back pain has a direct and proportional impact on function and a general one on the quality of life. The present study aims to evaluate the functional impact of low back pain using specific self-assessment tools as indexes of appreciation and epidemiological correlations of potential risk factors involved. The conceptual model of our research is based on the importance of correlating

symptoms with clinical assessment, using scales of pain, disability, quality of life, and determination of epidemiological correlations of these areas and the determined factors of the pathology (4).

The Orthopedic Section of the American Physical Therapy Association (APTA) has an ongoing effort to create evidence-based practice guidelines for orthopedic physical therapy management of patients with musculoskeletal impairments described in the World Health Organization's International Classification of Functioning, Disability, and Health (ICF).

Material and method

The study group is made up of 106 cases with clinical diagnostic of low back pain, admitted from 28 September 2020 to 28 March 2021, at Balneal and Rehabilitation Sanatorium of Techirghiol. After performing anamnesis, general clinical examination, specific neuro-musculo-skeletal examination, the patients filled the surveys highlighting the impact of their low back pain on functionality and disability deriving from it. The survey included the Oswestry Disability Index, the Functional Independence Measure (FIM) instrument and the Visual analog scale (VAS) score evaluated at the moment of hospitalization and at discharge. Statistical analysis of data was carried out and correlations between variables resulting from study were highlighted.

The Oswestry Disability Index (ODI) has been developed to assess pain-related disability in people with acute, subacute, or chronic low back pain. Since it was first published in 1980, several different versions have been developed The ODI covers 1 item on pain and 9 items on activities of daily living (personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling), making a total of 10 items. The ODI has adequate content validity, as it covers activities of daily living that are commonly experienced by patients with back pain. However, it lacks generic activities such as work, leisure, recreation, or sporting activities. The ODI has high internal consistency, with Cronbach's alpha between 0.71 and 0.87. It correlates with other measures of disability, such as the Roland-Morris Disability Questionnaire (RDQ) and shows moderate correlation with pain scales and the Short Form. Administration of the ODI questionnaire over the phone has excellent test-retest reliability when compared to face-to-face administration. Telephone administration is a convenient and reliable option for obtaining follow-up outcomes data. Telephonic administration of the ODI is scientifically valid and should be an accepted method of data collection for state-level and national-level outcomes projects (5-7).

The Functional Independence Measure (FIM) score is just one of many tools that clinicians can use to determine independence or amount of assistance needed in a rehabilitation setting as well as after discharge. The FIM was also developed to offer a uniform system of measurement for disability based on the International Classification of Impairment, Disabilities and Handicaps for use in the medical system in the United States (McDowell & Newell, 1996). The FIM assesses six areas of function (Self-care, Sphincter control, Transfers, Locomotion, Communication and Social cognition), which fall under two Domains (Motor and Cognitive). It has been tested for use in patients with stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, and elderly individuals undergoing inpatient rehabilitation and has been used with children as young as 7 years old. The FIM consists of 18 items assessing 6 areas of function. The items fall into two domains: Motor (13 items) and Cognitive (5 items). The motor items are based on the items of the Barthel Index. These domains are referred to as the Motor-FIM and the Cognitive-FIM (8).

The patients admitted underwent specific rehabilitation treatment which included a wide range of therapies. All patients received balneotherapy with the use of the local natural sources – the mineral water of the lake Techirghiol and also peloid therapy using the sapropelic mud extracted from the bottom of the lake. Electrotherapy varied from low, medium and high frequency electrical currents. The patients also underwent kinetotherapy and kinesiotherapy with the assistance of specialized physiotherapists

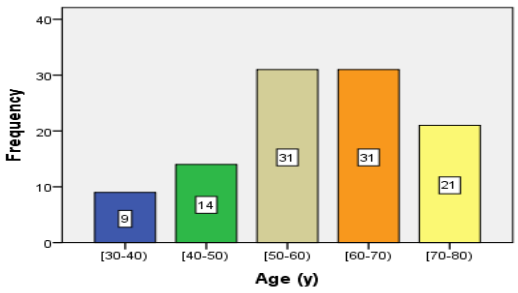
Results

Lumbar pathology is common in patients who are hospitalized for a complex balneal-physical-kinetic treatment at Balneal and Rehabilitation Sanatorium Techirghiol

The majority of patients were females, representing 57,55% of the total number. Regarding the patients' age, 58,5% of them were in the 50-70 years interval.

Table 1 – Total Score Oswestry Questionnaire - Spearman's rho

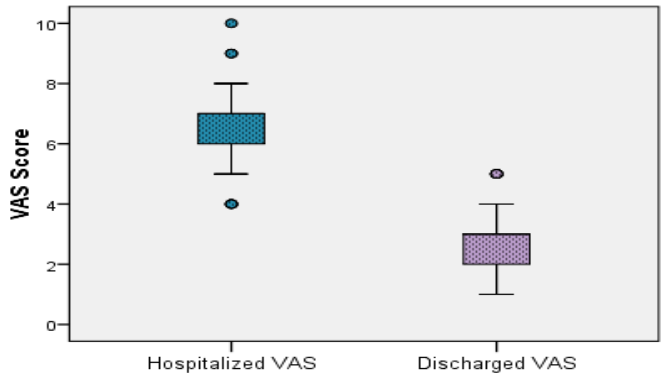
Spearman's rho	Correlation Coefficient	Sig. (2-tailed)	N
Pain intensity	.513	.000	106
Personal care	.576	.000	106
Lifting weights	.623	.000	106
Walking	.715	.000	106
Clinostatism	.685	.000	106
Orthostatism	.768	.000	106
Sleep	.562	.000	106
Sexual life	.313	.001	106
Social life	.670	.000	106



Graph 1 – Age interval distribution

Regarding the urban/rural distribution- 74,53% of the patients were from urban areas, perhaps also due to the easier accessibility to medical services, in general

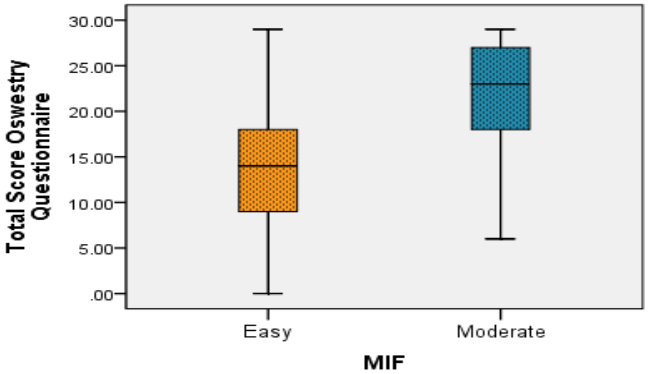
The study reveals a major positive impact of our treatment on spinal symptomatology, an effect pointed out by the relevant statistical differences between the admittance and discharge VAS scores($p<0.001$).



Graph 2 - Box-Plot representation of the distribution of VAS scores at admission and VAS at discharge

There are significant differences between median VAS scores at admission and discharge ($p <0,001$, Wilcoxon signed-rank test). Admission VAS scores were higher than discharge VAS scores.

Reporting the investigated disability with the Oswestry questionnaire of painful lumbar syndrome, and functional evaluation scale (FIM) demonstrates the impact of this pathology on the patient's social life, once again emphasizing the special attention to be paid to axial pathology, both as curative treatment and the importance of prophylactic treatment. Statistical analysis of identified risk factors reveals the importance of prophylaxis and patient's education in this area.

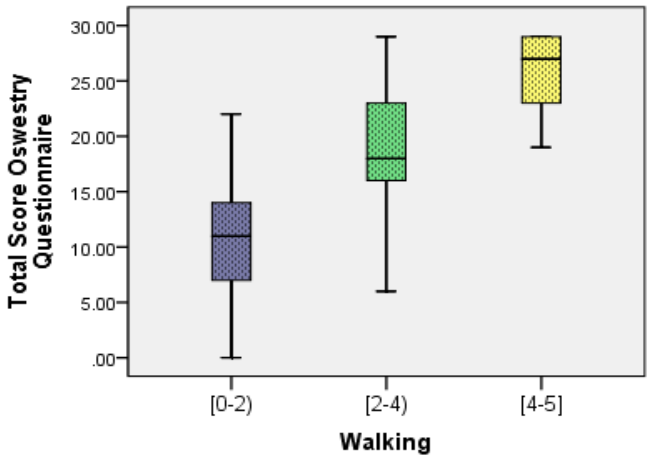


Graph 3 - Box-Plot representation of the distribution of MIF and Oswestry Total Score Questionnaire

A strong and important statistical correlation was found between the Oswestry total score and the walking and standing items, and a moderate, but strong correlation with the other items. Regarding the sex life item, the correlation is existent, but at a modest level.

There are significant differences between the median values of the Oswestry scores corresponding to the three groups Walking [0-2)/[2-4]/[4-5]] ($p = 0 <0,05$, Independent Samples Median *test).*

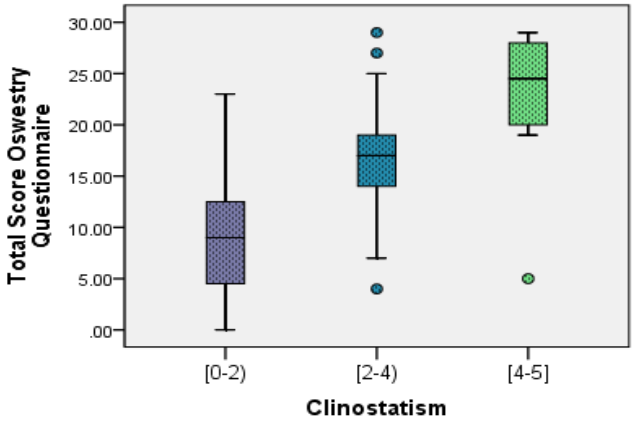
The distribution of scores Oswestry differed in the Walking [0-2]/[2-4]/[4-5]] groups, scores Oswestry were higher in the Walking [4-5] group than in the Walking [0-2] and Walking [2-4]] groups



Graph 4 - Box-Plot Representation of Oswestry Questionnaire Total Score Distribution and movement

There are significant differences between the median values of the Oswestry scores corresponding to the three groups Clinostatism [0-2)/[2-4]/[4-5]] ($p = 0 <0,05$, Independent Samples Median test).

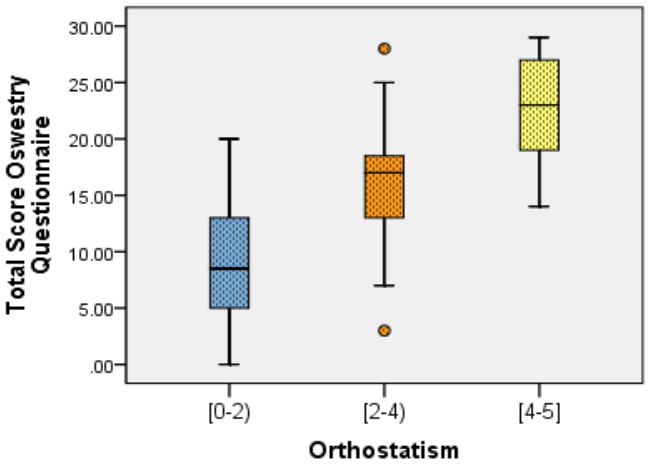
The distribution of scores Oswestry is different in the three Clinostatism groups [0-2)/[2-4]/[4-5]], the Oswestry scores were higher in the Clinostatism [4-5] group than in the Clinostatism [0-2) and Clinostatism [2-4)] groups.



Graph 5 - Box-Plot Representation of Oswestry Questionnaire Total Score Distribution and Clinostatism

There are significant differences between the median values of the Oswestry scores corresponding to the three groups Orthostatism [0-2)/[2-4]/[4-5]] ($p = 0 <0,05$, Independent Samples Median test).

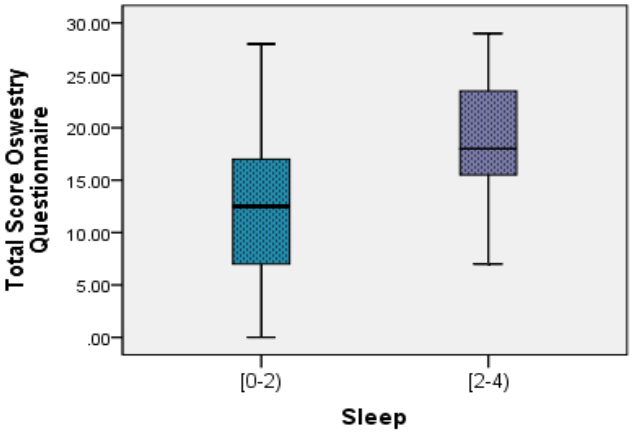
The distribution of scores Oswestry is different in the three Orthostatism groups [0-2)/[2-4]/[4-5]], the Oswestry scores were higher in the Orthostatism [4-5] group than in the Orthostatism[0-2) and Orthostatism [2-4)] groups.



Graph 6 - Box-Plot Representation of Oswestry Questionnaire Total Score Distribution and Standing

There are significant differences between median Oswestry values, corresponding to the two groups Sleep [0-2)/[2-4) (p = 0 <0,05, Independent Samples Median test).

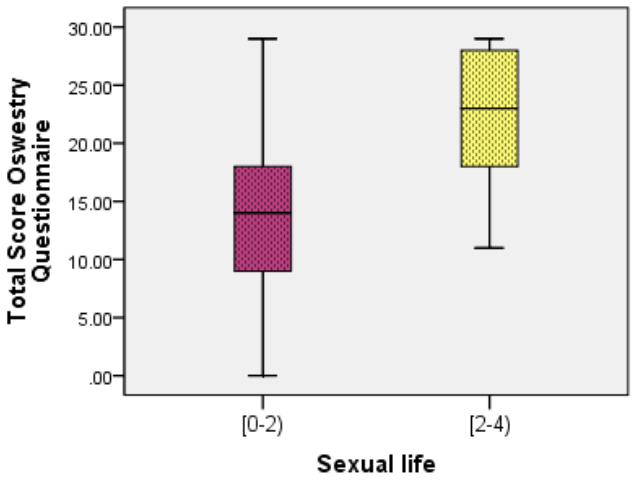
The distribution of scores Oswestry differed in the two Sleep [0-2)/[2-4)] groups, scores Oswestry were higher in the Sleep [2-4)] group, with values ranging from 15-20, than in the Sleep [0-2)] group, with values ranging from 6-17



Graph 7 - Box-Plot Representation of Oswestry Questionnaire Total Score Distribution and Sleep

There are significant differences between median Oswestry values, corresponding to the two groups Sexual Life [0-2)/[2-4) (p = 0 <0,05, Independent Samples Median test).

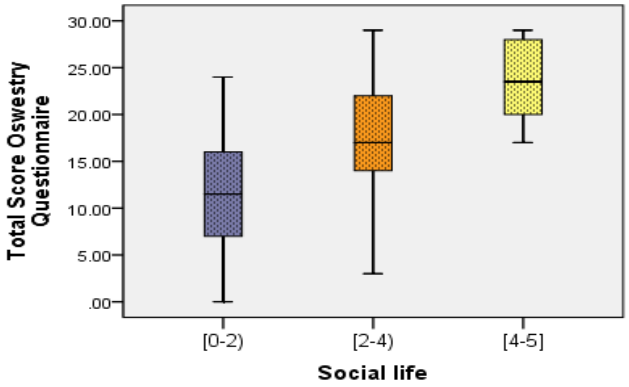
The distribution of scores Oswestry is different in the two Sexual Life groups [0-2)/[2-4)], scores Oswestry were higher in the Sexual Life [2-4) group, with values ranging from 18-28, than in the Sexual Life [0-2) group, with values ranging from 9-18.



Graph 8 - Box-Plot Representation of Oswestry Questionnaire Total Score Distribution and Sexual Life

There are significant differences between the median values of the Oswestry scores corresponding to the three groups Social Life [0-2)/[2-4]/[4-5]] (p = 0 <0,05, Independent Samples Median test).

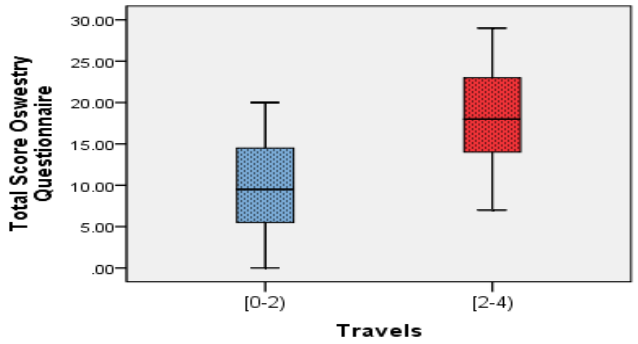
The distribution of scores Oswestry is different in the three Social Life groups [0-2)/[2-4]/[4-5]], the Oswestry scores were higher in the Social Life[4-5] group than in the Social Life [0-2) and Social Life [2-4)] groups.



Graph 9 - Box-Plot Representation of Oswestry Questionnaire Total Score Distribution and Social Life

There are significant differences between median Oswestry values, corresponding to the two groups Travels [0-2)/[2-4) (p = 0 <0,05, Independent Samples Median test).

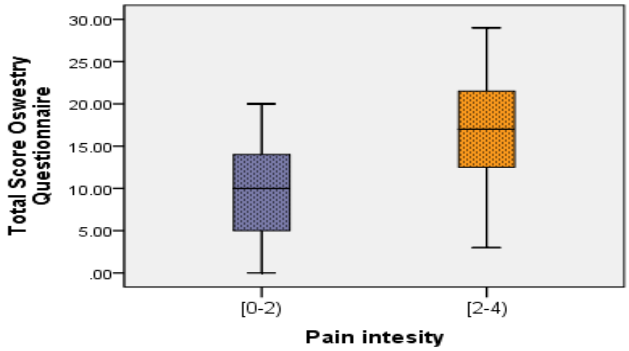
The distribution of scores Oswestry differed in the two Travels [0-2)/[2-4)] groups, scores Oswestry were higher in the Travels [2-4)] group, with values ranging from 15-23, than in the Travels [0-2)] group, with values ranging from 5-15.



Graph 10 - Box-Plot representation of the distribution of the Oswestry Questionnaire Total Score and Travels

There are significant differences between median Oswestry values, corresponding to the two groups Pain intensity [0-2)/[2-4) ($p = 0,001 < 0,05$, Independent Samples Median test).

The distribution of Oswestry scores differed in the two Pain intensity [0-2)/[2-4)] groups ($p < 0,001$, Independent Samples Mann-Whithney U test), Oswestry scores were higher in the Pain intensity [2-4)] group than in the Pain intensity [0-2)] group



Graph 11 - Box-Plot representation of the distribution of Oswestry Total Score Questionnaire and pain intensity

Discussions

The results show a clear predominance of low back pain in female patients as opposed to males, which needs to be addressed if it has true gender preponderance or is given by a population disbalance in favor of more females than males (4,9-12). As we can see, the age distribution is mostly in late adulthood and early elderhood, but nevertheless the balance is towards more advanced age, clearly suggesting a degenerative problem (13). Almost three quarters of the patients come from urban setting, which is due most likely to the access to medical services, as opposed to rural population who, by the nature of rural lifestyle, should have a distribution in accordance with rural/urban general distribution.

During the hospitalization period, with the help of the specific rehabilitation therapies, we observed a clear reduction of the algic syndrome, a thing that was reported by all patients by the means of the common VAS pain score. As the pain subsided, the general mobility has improved, with a direct influence over the overall functionality (14), as shown by the functional evaluation scale, indicating that the balneotherapy and the usage of physical therapy might be useful as a prophylactic treatment, not only as curative treatment (15,16).

After analyzing the distribution of the total Oswestry score and comparing it with each individual item, we observe that low back pain affects proportionally each aspect of the patient life. Similar distributions of the patients in 3 groups were found for the walking, standing, lying down and social life, and in 2 groups for sleeping, sexual life, travelling, and pain intensity. We know that a cause of insomnia is chronic pain, and we observed an improvement of the quality in sleep as we managed to decrees the pain felt in LBP syndrome (17,18), and it should be monitored on a longer period of time to verify if it is a consistent improvement. We should take into consideration the specific socio-economical factors of the Romanian nationality patients when analyzing some aspects of the everyday life such as sexual life (19) which has shown a clear improvement, but still with a notable dissatisfaction (from social viewpoint, as there is certain stigma about this essential aspect of life) and travelling (from the economical perspective, is quite prohibitive), which also showed a statistically relevant improvement(20). The clearest affliction is observed at patients in standing position, where they felt it has the greatest impact of the overall quality of life in comparison with all the other aspects of life (21). We can also see that the patients had a more direct approach when it comes the pain intensity with either considering the pain to be a big problem or a small nuisance that they could live with it, aspects shown in many other clinical studies from this field (22-26).

Conclusions

The study reveals the importance of correlation of the data obtained clinical exam with self-assessment tools, that determine the level of functional independence and the functional impact on social life. It is necessary to quantify the therapeutic results obtained, in order to assess the level of improvement in quality of life.

Low back pain (LBP) is the second leading cause of disability in the world. The level of disability in patients with LBP is an important outcome measure for clinical practice and research (27,28). The Oswestry Disability Index (ODI) is one of the most commonly used scales that assess the disability related to LBP.

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WATER, NATURE, TECHIRGHIOL – LONG-TERM THERAPEUTIC BENEFITS FOR PATIENTS WITH DEGENERATIVE LOW BACK PAIN

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Abstract. Exercise programs in water is an effective therapy for chronic low back pain. The aim of our study is to evaluate the impact of hydro-kinetotherapy in the salty water of Techirghiol lake, on patients with degenerative low back pain. We evaluated 50 patients admitted to Balneal and Rehabilitation Sanatorium of Techirghiol, before and after 2 weeks of therapy. The patients were divided into 2 groups, one group had hydro-kinetotherapy in the lake (hydro-kinetotherapy group – HKT), and the other group had no kinetotherapy (control group – CG). Both groups had electrotherapy (low, medium and high frequency currents, magnetic therapy, ultrasound therapy, laser therapy) and massage. Each patient had to complete a questionnaire regarding lumbar disability (Roland-Morris questionnaire), and during the physical examination we completed the Back Performance Scale and Visual Analogue Scale. We discovered statistically significant differences between the 2 values for both groups, but the values were more significant for the hydro-kinetotherapy group of patients (p value < 0.02). Our study reached the same results as the other studies, so hydro-kinetotherapy in salty water among special rehabilitation treatment improve the lumbar disability and also decrease the painful syndromes and dysfunction for patients with degenerative lumbar pathology.

Keywords: lumbar pain, Techirghiol lake, exercise.

AIMS AND BACKGROUND

Techirghiol Lake is located in Romania, in Dobrogea District, at 16 km from Constanta, near Eforie Nord on Lake Techirghiol shore, in a region with a mean altitude of about 200–300 m, situated between the lower Danube River and the Black Sea. The lake is in a temperate continental climatic area with an important influence of the sea (Fig. 1). The depression occupied by the lake was formed as fluvial-maritime lagoon during the last glacial periods[1].

* For correspondence.

Fig. 1. Techirghiol lake (our private photo)

Fig. 2. Sapropelic Mud from Techirghiol lake (our private photo)

The water of the lake has an important characteristic due to the variable concentrations of salt, which varies between insignificant salinity to 60, even 85 g/l. Water of the lake is greenish due to the numerous microorganisms and algae. The main alga that grows here is Cladophora. The pH of the water is alkaline between 7.8 and 8.3. Beside the alga, Techirghiol lake has a very prolific phyllopod crustacean, named Artemia salina which lives in the water during the warm season, from April until September[1]. Artemia salina feeds on micro plankton and contributes to the formation of mud (Fig. 2), depositing on the bottom of the lake after completing its life cycle[1,2]. The average annual temperatures range between 11°C along the Danube to 11.8°C on the coast and less than 10°C in the higher parts of the region[1]. The sapropelic mud, among the salty water, is an important

natural factor that has a high curative importance. The natural factors from Techirghiol area are extensively researched in various studies, especially in terms of therapeutic benefits for the patients treated in the Balneal and Rehabilitation Sanatorium of Techirghiol. Water may have therapeutic properties under different circumstances, such as Techirghiol lake water, but it can sometimes be a vehicle for transmitting different germs[3,4].

Low back pain is an important factor causing long-term disability. Although there are low back pain episodes which resolve rapidly, there are a lot of patients that suffer of chronic low back pain. Chronicity is due to the duration of over 12 weeks of pain. This has a significant impact on patient quality of life[5]. The prevalence of low back pain is increasing, and it is considered that approximately over 80% of the population suffer from this condition. It is considered the fifth most common reason for visiting a physician and it is also the most common cause of disability in patients between 45 and 65 years old and it seems that the prevalence of these pathology is higher in women[5]. In terms of risk factors the most commonly and frequently are: high levels of psychological distress, low levels of physical activity, smoking, obesity. Chronic low back pain has multiple causes, divided into 3 main categories: mechanical low back pain (90%), non-mechanical spinal conditions and visceral disease. Mechanical low back pain is defined as pain caused by trauma or deformities of anatomic structures. These conditions are aggravated due to inappropriate physical activity. Causes of mechanical low back pain are: lumbar strain, sprain, degenerative processes, herniated disc, spinal stenosis, osteoporotic compression fracture, spondylolisthesis, traumatic fracture, congenital disorders, severe scoliosis, severe kyphosis, transitional vertebrae, spondylosis, internal disc disruption, presumed instability[5].

Hydrotherapy or aquatic exercise is a very useful treatment for patients with low pain or with other musculoskeletal or neurological conditions. Recent studies revealed positive effects for middle-age and elderly people[6]. This research showed that patients with chronic low back pain are obese, have a deficiency of mobility and endurance. Exercise programs in water are an effective therapy for chronic low back pain. These programs, according to the recent studies, reduce the incidence of painful episodes, increase muscle strength, increase flexibility of the spine and of the whole body, and improve the quality of life of patients with this pathology. Aquatic exercise is facile because all body weight is discharged into water and is an easier way to exercise for patients with low back pain. Each program can be improved and adapted for each patient[7]. These studies[6–10] had evaluated patients with low back pain who performed aquatic exercise in freshwater, but we proposed to evaluate patients who performed hydro-kinetotherapy in the salty water of Techirghiol lake and also performed rehabilitation treatment.

EXPERIMENTAL

The aim of our study is to evaluate the impact of hydro-kinetotherapy in the salty water of Techirghiol lake, during summer time, on patients with degenerative low back pain. We evaluated 50 patients with degenerative low back pain, admitted to Balneal and Rehabilitation Sanatorium of Techirghiol, for a period of 2 weeks. Each patient received an informed consent and oral instructions about the study and the protocol. The patients were evaluated paraclinically and clinically before and after 2 weeks of therapy. The patients were divided into 2 groups, one group had hydro-kinetotherapy in the lake (hydro-kinetotherapy group – HKT), and the other group had no kinetotherapy (control group – CG). Both groups had electro-therapy (low, medium and high frequency currents, magnetic therapy, ultrasound therapy, laser therapy) and massage. Each patient had to complete a questionnaire regarding lumbar disability (Roland-Morris questionnaire – RM), and during the physical examination we completed the Back performance scale (BPS) and Visual analogue scale (VAS). These parameters were completed before and after the treatment for each patient. The study groups had been analysed by age, gender, provenance, pathology, history of disease, frequency of balneal treatment, body mass index. We included in the study patients with low back pain, with a history of pain of minimum 12 weeks, with degenerative causes of low back pain. Exclusion criteria were: major rheumatologic, neurologic, cardiovascular, respiratory, renal, digestive conditions, presence of inflammatory syndrome (elevation of: erythrocyte sedimentation rate, fibrinogen), malignant diseases, presence of any psychiatric disorder, pregnancy or recent childbirth, any sign or symptom that might suggest serious medical illness, any skin disorders.

Patients from the hydro-kinetotherapy group had to perform a specific program in the salty water of Techirghiol lake. The exercises were done in the lake during the summer time, the temperature of the water was approximately 23–25^{o}C and the temperature outside was within 28–32^{o}C. Each hydro-kinetotherapy session lasted 50 min, the patients were closely supervised by a kinetotherapist. Each session included 10 min of warm-up, 15–20 min of aerobic exercises, 10 min of resistance exercises and 10 min of stretching exercises.

Statistical interpretation of the results of the study was performed using SPSS 22.0 programme.

RESULTS AND DISCUSSION

Analysing the groups from the study we find that from the control group (CG) out of 25 patients, 16 were female (64%) and 9 were male (36%), and from the hydro-kinetotherapy group (HKT), 13 were female (52%) and 12 were male (48%), which confirms that the prevalence of this pathology is higher for women[5]. Regarding the age of the patients, in the control group (CG) patients were between 45 and

67 years old, with a mean of 58.72 years, and in the second group (HKT) patients were between 44 and 65 years old, with a mean of 56.36 years (Table 1).

Table 1. Age of patients in the two groups from the study

Group		*N*	Minimum	Maximum	Mean	Std. deviation
CG	Age	25	45	67	58.72	6.275
HKT	Age	25	44	65	56.36	6.645

Majority of the patients are from urban provenance, as shown in Table 2, the whole control group and 21 patients from the hydro-kinetotherapy group.

Table 2. Characteristics of the CG and HKT group of patients from the experimental study

Characteristics of the groups		Group				*p**
		CG		HKT		
		count	%	count	%	
	total	25		25		
Patient gender	woman	16	64.0	13	52.0	0.390
	men	9	36.0	12	48.0	0.390
Pathology	spondylosis	15	60.0	13	52.0	0.569
	spondylolisthesis	3	12.0	3	12.0	1.000
	lumbar discopathy phase II	3	12.0	5	20.0	0.440
	Lumbar disc herniation	4	16.0	4	16.0	1.000
Provenance	Urban	25	100.0	21	84.0	0.037
	Rural	0	0.0	4	16.0	0.037
History of disease	0–6 months	0	0.0	2	8.0	0.149
	> 6 months	25	100.0	23	92.0	0.149
Frequency of balneal treatment	biannual	0	0.0	0	0.0	–
	annual	9	36.0	15	60.0	0.089
	occasional	13	52.0	0	0.0	0.000
	first time	3	12.0	10	40.0	0.024
BMI interval	normal	9	36.0	3	12.0	0.047
	obesity	16	64.0	22	88.0	0.047

*Chi-squared test for the comparison of two proportions.

Regarding the average age of the disease, almost all the patients had the low back pain pathology over 6 months, all patients form the control group and 23 patients form the second group of patients. In terms of the distribution of patients by frequency of balneal treatment we discovered that no patients did the rehabilitation treatment biannual, as indicated, patients that had each year treatment were 9 patients (36%) from the first group and 15 patients (60%) from the second group,

occasional treatment did 13 patients (52%) from the first group and no patient from the second group, and for the first time we had 3 patients (12%) from the first group and 10 patients (40%) from the second group. Analysing the body mass index (BMI) of the patients in the study we had only 9 patients (36%) from the first group and 3 patients (12%) from the second group which had a normal BMI, the other patients were overweight or with obesity. This is a worrying number of patients with obesity, which confirms once again the previous studies[5] regarding the fact that obesity is a risk factor for low back pain. Analysing the groups regarding the pathology of the patients, we noticed that spondylosis had 60% of patients from the control group and 52% of patients from the hydro-kinetotherapy group, lumbar disc herniation is the same in both groups 16% of patients, spondylolisthesis 12% of patients in both groups, and lumbar discopathy is 12% in the first group and 20% (Ref. 8) in the second group. We do not have a pattern regarding degenerative low back pain, as we mentioned above there are no studies conducted on the prevalence of the causes of low back pain and we have few patients in our group in order to conclude that this could be the pattern of the prevalence of degenerative low back pain (Table 2). In terms of demographic characteristics there are no statistically significant differences between female proportion from both groups or any other categories (males, provenance, history of disease, pathologies, frequency of treatment, etc.) from the demographic characterisation table (Table 2).

In our study we measured VAS for pain in the first day of treatment and in the last one. VAS is a commonly used scale used to monitor the patient pain or the response to a pain treatment. It is a subjective measurement, the patient respond with a mark between 1 and 10 regarding the level of pain that he has. 1 is for no pain, and 10 is for severe, insupportable pain. Analysing VAS scores for groups in the study, we noticed that the distribution of VAS scores before treatment (VAS1) ($p = 0.370$), and the distribution of VAS scores after treatment (VAS2) ($p = 0.547$) is the same in the control group and in the hydro-kinetotherapy group, so there are no significant differences between the scores obtain for the VAS scores (VAS1 and VAS2) measured in the two groups (Figs 3 and 4, Table 3).

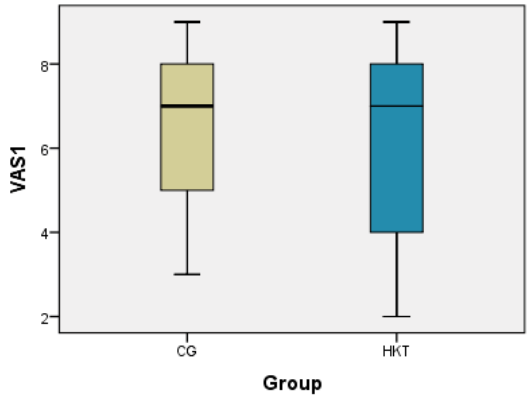

Fig. 3. Box-Plot representation of VAS1 values for the two groups from the study

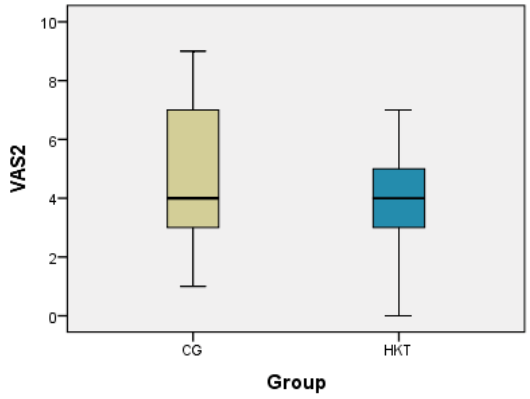

Fig. 4. Box-Plot representation of VAS 2 values for the two groups from the study

Table 3. *p* Values for the VAS scores, RM values and BPS values for the CG and HKT group of patients from the experimental study

Values of VAS, RM and BPS	Differences between CG and HKT (*p* values)	CG (*p* values)	HKT (*p* values)
VAS1	0.370		
VAS2	0.547		
Median differences between VAS1 and VAS2		<0.001	<0.001
RM1	0.619		
RM2	<0.020		
BPS1	0.600		
BPS2	0.401		
Median differences between BPS1 and BPS2		0.546	<0.001

But if we analyse the VAS scores before and after the treatment separately for each group we noticed that also for the control group and for the hydro-kinetotherapy group there are statistically significant differences between mean VAS scores before and after the treatment ($p < 0.001$) as it can be observed from the Box-Plot representation (Figs 5 and 6, Table 3), VAS scores after the treatment are significantly lower than VAS scores values before treatment (Table 3).

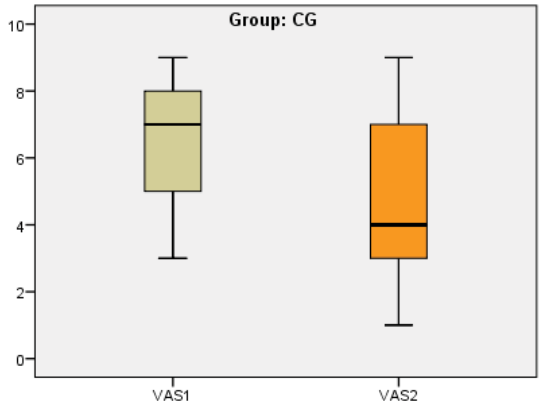

Fig. 5. Box-Plot representation of VAS1 and VAS2 scores for group CG

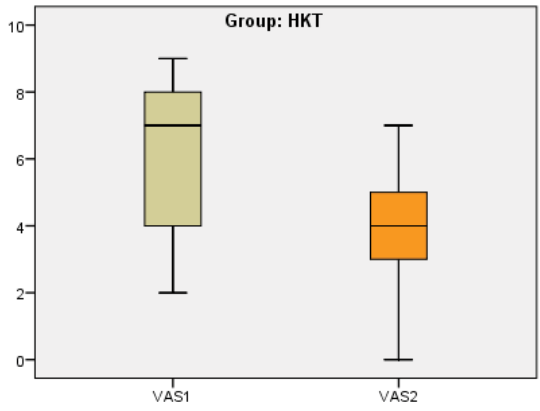

Fig. 6. Box-Plot representation of VAS1 and VAS2 scores for group HKT

In our study we used a disability questionnaire specific for lumbar pathologies the Roland Morris (RM) questionnaire. The patients from the study groups completed this questionnaire before and after the treatment. Roland-Morris questionnaire has 24 affirmations regarding diverse activities that each one is doing as a regular basic (if the pain is almost all day, if the pain affects the sleeping hours, or affects the appetite, if the pain appears when sitting or standing, or lifting, etc.). Analysing the Roland Morris questionnaire before (RM1) and after the treatment

(RM2) for the two groups of patients, we discovered statistically significant differences between the 2 values for both groups, but the values were more significant for the hydro-kinetotherapy group of patients (p value < 0.02) (Figs 7 and 8, Table 3).

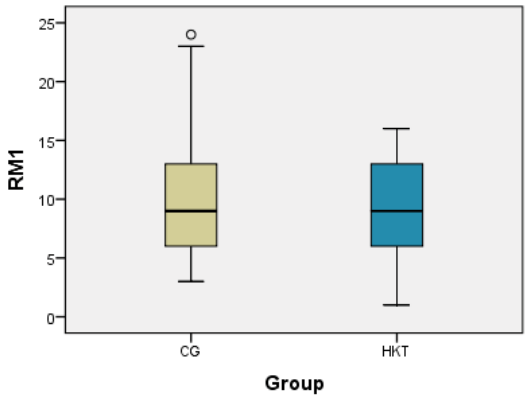

Fig. 7. Box-plot representation of RM1 values for the two groups of our study

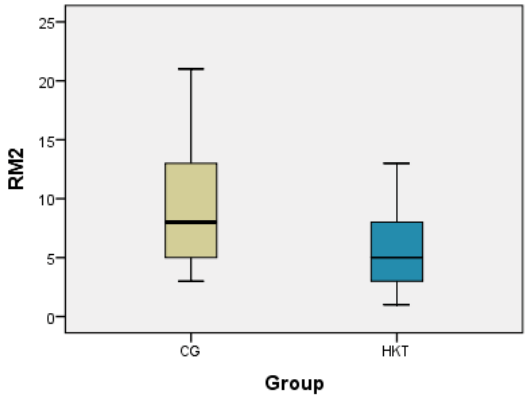

Fig. 8. Box-plot representation of RM2 values for the two groups

In order to evaluate the mobility of each patient, we used the Back performance scale before (BPS1) and after the treatment (BPS2). This scale is composed by 5 tests: sock test, pick-up test, roll-up test, fingertip-to floor test and lift test. All tests require mobility of the trunk and there are performed from sitting, standing or lying positions[11]. For each test the patient has a task, for example for the sock test, the patient is sitting on a firm bench, with the feet not reaching the floor, and he has to grab the toes with fingertips of both hands. For each test the patient gets a score from 0 to 3. We analysed the results for each group in comparison and we discovered that the distribution of BPS scores before the treatment (p = 0.600) and the distribution of BPS scores after the treatment (p = 0.401) is the same for

each group in the study, so there are no significant differences between the scores of BPS measured for the two groups (Figs 9 and 10, Table 3).

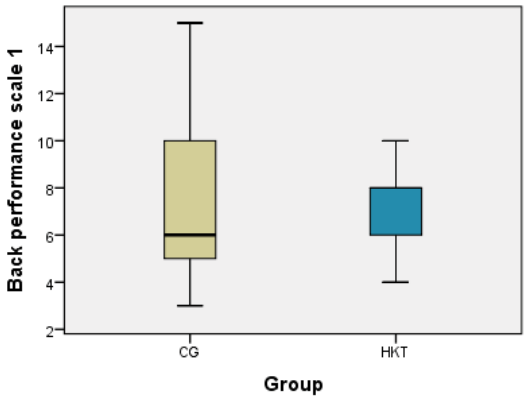

Fig. 9. Box-plot representation of BPS1 scores for CG and HKT groups

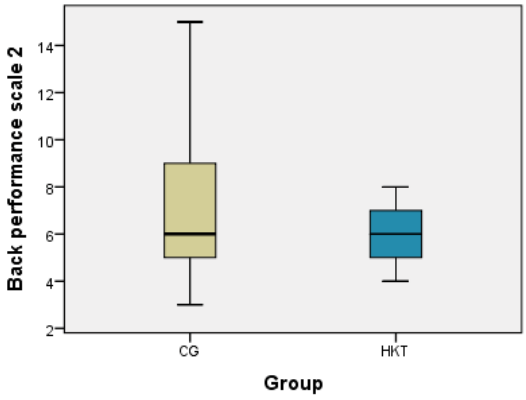

Fig. 10. Box-plot representation of BPS2 scores for CG and HKT groups

We also evaluated BPS scores separately for each group and we discovered that for the control group there is no statistically significant differences between the median values of the BPS scores before and after the treatment ($p = 0.546$) (Table 3). For the hydro-kinetotherapy group there are statistically significant differences between the median values of the BPS score before and after treatment ($p < 0.001$) (Table 3), and as seen from the associated Box-Plot representation, BPS scores after treatment are significantly lower than the BPS score before treatment (Figs 11 and 12, Table 3).

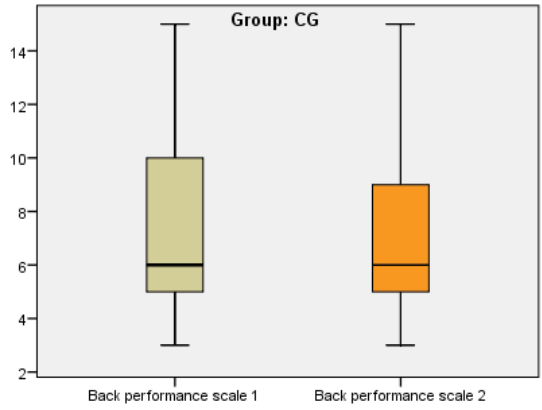

Fig. 11. Box-plot representation for BPS1 and BPS2 scores for CG group

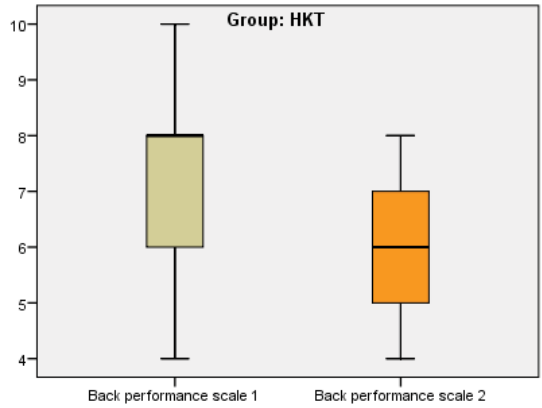

Fig. 12. Box-plot representation for BPS1 and BPS2 scores for HKT group

CONCLUSIONS

As previous studies conducted which analysed the lumbar disability (with RM questionnaire)[9–12], our study reached the same results as the others, so hydro-kinetotherapy in salty water among special rehabilitation treatment improve the lumbar disability for patients with degenerative lumbar pathology. Although we did not have statistically significant differences between the two groups regarding the VAS scores before and after the treatment, we had significant differences between the 2 values of VAS scores for each group (CG and HKT group), that highlights the fact that rehabilitation treatment without any physical activities decreases the level of pain in patients with degenerative low back pain. Regarding the BPS scores, although we did not have statistically significant differences between the two groups, we noticed that only in the hydro-kinetotherapy group we had statistically

significant differences between BPS scores before and after the treatment, which highlights that aquatic exercises in the salty water of Techirghiol Lake improve the mobility of patients with degenerative low back pain. Until now there were no studies[13] conducted on aquatic exercises performed in natural salty water and we believe that it is an important natural factor that it is provided to us in this region[14].

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