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METHODS INVOLVED IN AMENDING PAIN OF THE LUMBAR SPINE DEGENERATIVE PATHOLOGY

PHD THESIS SUMMARY

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INTRODUCTION

Degenerative pathology of the lumbar spine is common in medical practice, because it manifests itself from an early age, causes discomfort to the patient and even causes disability. Pain is the most common symptom in the clinical manifestation of degenerative pathology, it is which causes the patient to go to the doctor for a medical check-up and its approach is multidisciplinary.

Chronic low back pain is an intensely researched topic, and the treatments applied to reduce the pain are multiple, from drug treatments to rehabilitation treatments with real benefits to surgical treatments. Although degenerative pathology is an important cause of chronic low back pain, and causes multiple consequences for both the patient and the health system, it requires more accurate reporting, based on better defined, more uniform terminology in order to develop a more efficient overall reporting [1].

The original element of this thesis is the quantification of two serum markers serotonin and BDNF (brain derived neurotrophic factor) which have not been used so far in research on patients with chronic degenerative lumbar pain under complex rehabilitation treatment.

The thesis is structured in two parts: **a general part** which includes the *current state of knowledge*, data on the *national and international situation* on the proposed topic, data on *epidemiology and etiopathogenesis, pathophysiology of pain in the pathology of the lumbar spine* and *methods of rehabilitation treatment for pain from degenerative pathology of the lumbar spine* and **the special part** that covers the *research objectives*, *working methodology*, and *results* obtained systematized in 3 studies - the first study evaluates the functionality of patients with low back pain after the applied treatments, the second study analyzes the evolution of serological markers serotonin and BDNF after rehabilitation treatments, and the third study analyzes the pain and quality of life of patients with degenerative lumbar disease.

The paper contains 44 images found in the thesis as follows: 4 in the general part, 10 in the methodology chapter showing the working method for the serological markers used, 9 images with types of rehabilitation treatments applied to the study patients and 21 images found in the special part of the thesis with statistical diagrams. In addition, there are 100 tables with statistical indicators used to quantify questionnaires, scales, indices and serological markers used in scientific research.

1. Working hypothesis / objectives

1.1. The purpose of the doctoral thesis

The aim of this thesis is to quantify the clinical and serological effects of complex rehabilitation methods on chronic degenerative pain of the lumbar spine and on the quality of life of the patients with this disease.

1.2. The objectives of the doctoral thesis

In order to achieve the purpose of the current thesis, we have elaborated the following objectives:

- To determine how **serum serotonin** is influenced after a complex rehabilitation treatment
- To determine how **serum BDNF / brain-derived neurotrophic factor** is influenced after a complex rehabilitation treatment course
- To determine the evolution of **low back pain** by quantifying it, using specific questionnaires and how it is influenced after rehabilitation treatment
- To determine how the **mobility of the lumbar spine** evolves after rehabilitation treatment
- To determine the evolution of the **quality of the life** of patients with chronic lumbar degenerative pain and how it is influenced after rehabilitation treatment

2. General methodology

2.1. Patient selection

The study was an observational, prospective and comparative clinical study on the therapeutic effects of the rehabilitation treatments. The study took place between 2015 and 2020. The patients were enrolled in the Balneal and Rehabilitation Sanatorium of Techirghiol, and the analysis of serological markers was performed in the laboratory within the Sanatorium and at a laboratory in Constanta. In order to enroll the patients in the study, the approval was obtained from the Sanatorium for the development of the research in the unit, and it was also obtained the approval from the Ethics Commission of the Institute of Doctoral Studies, regarding the research, the annexes being attached at the end of the thesis.

The selection of patients was made taking into account certain specific criteria:

- **Inclusion criteria**: patients with chronic low back pain (over 3 months), age over 18 years and patient consent.

- **Exclusion criteria**: age under 18 years, biological inflammatory syndrome at the time of enrollment in the study, any known chronic inflammatory conditions, chronic conditions decompensated at the time of enrollment in the study (cardiovascular, hepatic, renal, respiratory, neurological), pregnancy or lactation, skin trophic disorders, any infectious disease, neoplastic disorders, psychiatric disorders, allergies to natural factors that may cause discontinuation or interruption of natural factor treatments, or patient refusal.

2.2. Study procedure

In the present study, a number of 130 patients were enrolled, divided into 3 groups: 51 patients were part of the group with hot mud baths (BCN), 48 patients from the group with cold mud baths (BRN) and 31 patients were part of the control group (LM).

2.2.1 Clinical evaluation of patients

All subjects signed an **informed consent** form by which they agreed to participate in this study. Upon enrollment in the study, selected and eligible patients were evaluated using the following: **Questionnaire with patient data** - sex, age, height, weight, educational level, history of low back pain, frequency of balneo-physical-kinetic treatment; for assessing the degree of low back pain, patients completed the **Analogue Visual Scale (VAS)** and the **Pain Catastrophizing Scale (SCD); Disability Roland Morris Questionnaire (RM)** - questionnaire for assessing functional disability in chronic low back pain; **Quebec Lumbar Disability Scale (QB) and Oswestry Disability Index (ODI)** - questionnaires assessing disability due to chronic low back pain; **Short form 36 questionnaire (SF36)** - questionnaire that evaluates the quality of life; **General and spinal clinical examination** - patients were clinically evaluated and the **Back Performance Scale (BPS)** was used to assess spinal mobility and the **Schober test, finger-to-floor index (IDS), left (ILL left) and right (ILL right) lateral inflection** and the results were summarized in a completed form for each patient. All questionnaires, scales, assessments on spinal mobility were performed on the first and last day of treatment for each patient. All the forms used (informed consent and questionnaires / scales) are attached to the doctoral thesis.

2.2.2. Biological evaluation of patients

Patients in the study had the following biological samples: ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), FR (rheumatoid factor), blood glucose,

cholesterol, serotonin, and BDNF (brain-derived neurotrophic factor). Following the interpretation of the results, patients with biological inflammation syndrome were excluded from the study. The usual serum samples and specific markers - serotonin and BDNF were collected before and after treatment for each patient and were determined by ELISA method, the method described in the special part of the thesis, chapter Methodology.

2.2.3. Therapeutic methods used in the study patients

Patients enrolled in the study, according to the inclusion and exclusion criteria, underwent rehabilitation treatment: electrotherapy (with analgesic, muscle relaxant, neurovegetative system regulation, biotrophic, vasodilatory effect), underwater shower, paraffin poultices (for muscle decontraction) massage therapy and physiotherapy/kinetotherapy (Williams program in 3 phases, back school). The natural balneal treatment factors used in the study were mud, salty water of Lake Techirghiol and climate. The mud was used in one group as hot mud bath and in the second group as cold mud bath.

2.3. Statistical analysis

The data were processed using the Statistical Package for Social Sciences (SPSS) version 20. The procedures used were: elementary statistical analysis calculations: central tendency indicators and dispersion indicators, descriptive statistics for characterizing discrete and continuous variables defined at the base level data, Graphs, Parametric statistical tests, Nonparametric statistical tests. The results considered statistically significant were those for which a statistical p value <0.05 [2], [3], [4], [5], [6] was obtained.

3. Results

3.1. General characteristics of the patients in the study

The average age of the patients in the study was 55.71 in the group with hot mud baths, 56.81 in the group with cold mud baths and 56.97 in the control group. More than half of the patients in the study were female and mostly from urban areas. The share of overweight and obese patients was over 65% in all 3 groups of patients. More than half of the patients have higher education and are still professionally active. The history of lumbar pain in over 50% of them is over 5 years, with the onset of pain after lumbar overload, and the vast majority of patients in the study are sedentary. From the point of view of degenerative pathology, over half of them were diagnosed with lumbar spondylosis. The order of frequency was as follows: phase III lumbar discopathy, phase II discopathy and spondylolisthesis (Figure 1).

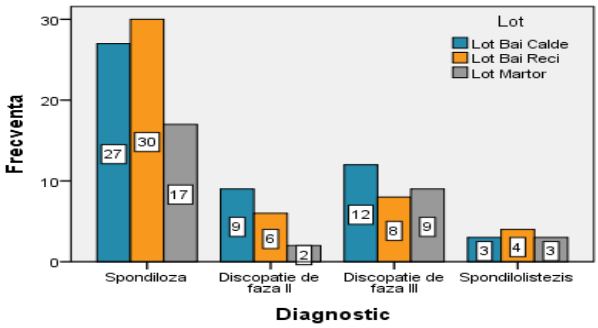

Figure 1 - Diagnosis of study patients

3.2. Study 1 - Evaluation of lumbar spine functionality in patients with chronic lumbar degenerative pain after complex rehabilitation treatment

The disability questionnaire Roland Morris (RM) recorded an improvement in its values after rehabilitation treatments, in all patients in the study, but in the control group the values were higher and their decrease was lower compared to the other two groups, but the differences were statistically significant in all groups ($p < 0.001$) (Figure 2).

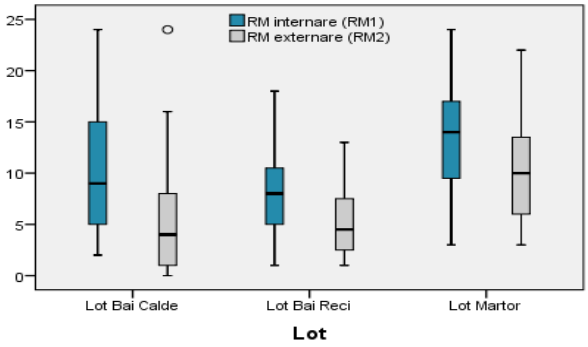

Figure 2 - Box-Plot representation of the values of the RM questionnaire in patients from the 3 groups

In the group with hot mud baths (BCN) the results were more significant than those in the group with cold mud baths (BRN) (the values being 3,498 higher in the BCN group). Patients over the age of 50, who are also the majority in this study, had predominantly higher values than those under the age of 50. And the statistical tests used (Median and Kruskal Wallis) showed us statistically significant differences in the median values and the distribution of the median values obtained in this questionnaire, only in patients over 50 years of age. The values given by both sexes are found to be comparable, and statistical tests show significant differences in both sexes. Normal weight and overweight patients obtained comparable values of the questionnaire, and the

decreases were statistically significant for both categories of patients and the distribution of median values in both normal and over-weight patients.

The Quebec lumbar disability scale (QB) recorded decreases in its discharge values compared to the first day of hospitalization values in all patients while higher values were recorded in patients in the control group; but the differences were significant in the 3 groups of patients. (P <0.001) (Figure 3). Both mud therapies improve the disability quantified on it. Median and Kruskal Wallis tests showed significant differences in patients over 50 years of age. In females, the scale values were higher than in males, and statistically significant values were recorded only in male patients. Regarding the weight of patients, there are higher values in overweight patients both at admission and discharge, in the 3 groups of patients, and the differences were significant in both categories of patients.

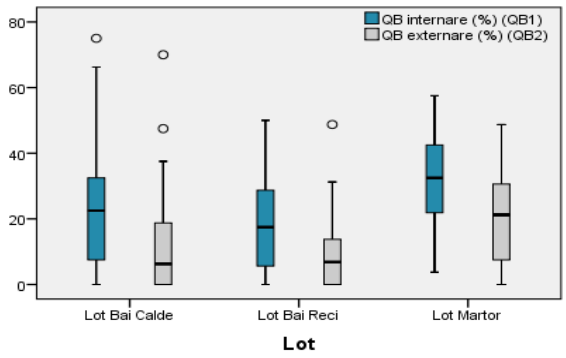

Figure 3 - Box-Plot graphical representation of the QB scale values for the 3 groups

The Oswestry Disability Index (OSW / ODI) recorded a statistically significant decrease in discharge values in all patients in the study (p <0.001) (Figure 4), but higher values were also recorded in the control group. This improvement was also recorded in the group of 25 patients who were part of the group with cold mud baths, the subject of an article published from this study, which also analysed the values of the RM questionnaire and the QB scale with the same trend od decreasing values after the rehabilitation treatment [7].

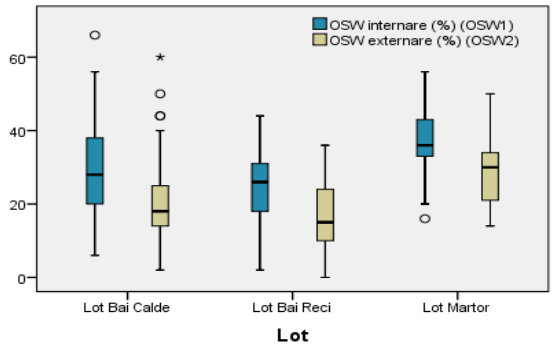

Figure 4 - Box-Plot representation of the ODI index values in the 3 groups in the study

Both mud therapies have the same effect on improving the index values. The values recorded in patients over 50 years of age were higher than the values recorded in patients under 50 years of age, but following the statistical tests applied (Median and Kruskal Wallis) the differences were significant only in patients over 50 years of age. Females recorded higher values on the first day of treatment than males, and the differences were significant for both sexes. Overweight patients recorded higher values at hospitalization than normal-weight patients. The differences were statistically significant in both categories of patients.

Back performance scale (BPS) values decreased statistical significantly for all patients in the study $p < 0.001$, and patients in the group with hot mud baths had a better response to decreased BPS values after the 10 days of treatment, compared to those who had taken cold baths. The BPS scale recorded higher values in patients over 50 years of age. Comparative values were recorded in both sexes, but only the male sex registered statistically significant differences in the admission and discharge of the scale values. Normal weight patients recorded significant values compared to overweight patients, both median values and the distribution of the median values at admission and discharge of the BPS scale.

Analysis of the **Schober index, finger-to-floor index (SDI) and latero-lateral** inflections shows an increase in the mobility of the lumbar spine after treatment, the differences were statistically significant for all indices.

A comprehensive analysis of the indices of disability or mobility of the lumbar spine in degenerative pathology has not been performed so far. Research in the field so far has analysed the evolution of disability indices in patients who have undergone assisted physical therapy [8], or yoga programs specifically adapted to chronic low back pain [9], [10], [11], [12], [13], [14], or balneal therapies with mud compress and bath in mineral-alkaline water [15] or baths with

mineral water [16], [17], or balneal-physical therapies [18]. As far as we know, there are no studies to assess signs of disability and mobility in patients with complex balneal-physical-kinetic rehabilitation treatment.

3.3. Study 2 - Assessing how serum parameters - serotonin and brain-derived neurotrophic factor (BDNF) - are influenced by a complex rehabilitation treatment regimen

This study is a continuation of study 1, in which a paraclinical analysis of serological markers that were collected on the first and last day of treatment was performed. The data were analysed and compared for each patient in the 3 groups in the study.

Serotonin is more commonly known to be closely related to neuropsychiatric syndromes, more exactly serotonin deficiency can cause various pathologies, such as depression, schizophrenia, mood disorders and even autism [19]. But it has been observed that serotonin is closely related to both chronic low back pain [20] and fibromyalgia, with lower serum levels in patients with these pathologies [21] than in healthy ones.

In our study it was observed that serum serotonin levels increase at discharge, after 10 days of therapy, compared to admission. The increases in values were higher in the patients who also benefited from mud therapies, compared to the patients in the control group, and the discharge values in the group with hot mud baths were higher than in the discharge values in the group with cold mud baths. The differences registered in the 3 groups were statistically significant, the p values being below 0.05 (Figure 5). There is little research on how serum serotonin develops in chronic lumbar degenerative pain. There is research that has shown the role of exercise in modulating serotonin, but also in reducing chronic pain [22], or effects of yoga-type exercises which in this case increase the level of serum serotonin [23], but up to now no study has been performed to examine the influence of complex rehabilitation therapies, which, in addition to specific physical therapy programmes and natural balneal treatments, associate also classical electrotherapy and massage therapies, on serum serotonin in patients with chronic lumbar degenerative disease.

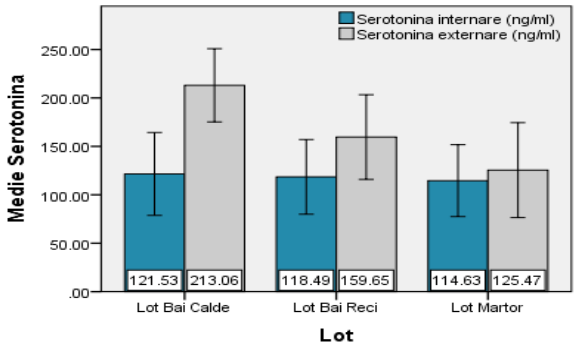

Figure 5 - Box-plot representation of serum serotonin values in the 3 groups

Serotonin decreases with age, in both females and males [24]. In our study, the values recorded in patients over 50 years were lower, compared to patients under 50 years of age. Although these differences were recorded between the two age groups, rehabilitation treatments had an effect in both categories, with statistically significant differences for all patients in the 3 groups studied. Serum serotonin values were approximately equal in women and men, slightly higher in females while normal-weight patients had higher values than the overweight or obese patients, as cited in other research [25], [26]. The fact that, although overweight patients had lower values at both admission and discharge than normal weight patients, at the end of treatment those with higher BMI had increased the serum serotonin levels is encouraging because it also means that these patients experienced a decrease in pain, this being one of the main goals of rehabilitation treatment.

BDNF serum/brain-derived neurotrophic factor is influenced by the patient's pathology. This is closely related to psycho-affective disorders, as well as to chronic low back pain. In a study performed on patients with chronic low back pain versus healthy patients BDNF serum levels were lower in those with chronic degenerative pathology [27]. BDNF is known to be influenced by exercise, its value increases after exercise, and is recognized as a therapeutic factor in the clinical expression of depression [28], [29]. A study conducted in Japan showed that elevated serum BDNF values are associated with a lower risk of cognitive decline [30].

In our study we highlighted the fact that after the rehabilitation treatments with natural factor (peloido-therapy, hydro-kineto-therapy in salty water) and kineto-therapy, the serum values of BDNF increase, compared to the control group where they had neither natural factor therapies nor kineto-therapy. This was also highlighted in two smaller groups of patients in our research, control group and hot mud bath group, where serum BDNF values increased in the

group that performed peloido-therapy [31]. The values recorded in the groups with mud baths were approximately equal, slightly higher in the group with cold baths, but insignificant compared to the group with hot baths. The differences in serum values recorded at discharge compared with hospitalization in the groups with peloido-therapy and kineto-therapy were statistically significant ($p < 0.05$) (Figure 6). Studies to assess the influence of complex recovery therapies have not been performed up to now. Only yoga programmes or physical exercises that increase serum BDNF values [23], [32], [33], [34] were approached.

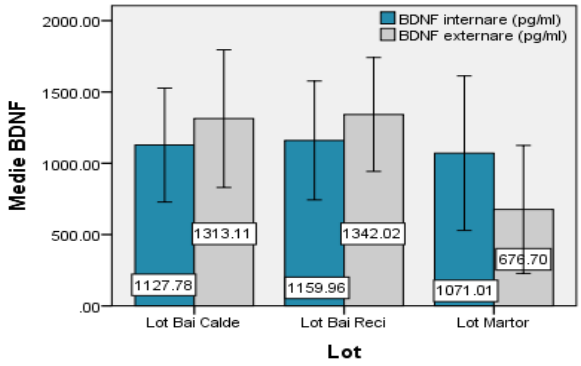

Figure 6 - Box-Plot representation of serum BDNF values for study patients

Research has so far shown that elderly patients have lower serum BDNF values than younger patients [35], [36], [37], which was also found in the present study, at admission and discharge. In both groups of patients, statistically significant values were found, more precisely the values increase post-treatment compared to the initial ones in patients in groups with hot baths and cold mud baths. Serum values in women are higher than in men [38], as we found in our study, both categories of patients registering statistically significant differences at discharge compared to admission. Serum BDNF is influenced by body weight; overweight patients have lower serum values than the normal weight ones [26], [39], which was observed in our study. Although this difference was recorded, patients in both categories responded to treatment, and in the groups with peloido-therapy, hydro-kineto-therapy and kineto-therapy there were statistically significant increases after treatment of serum BDNF values.

3.4. Study 3 - Evaluation of pain and quality of life of patients with chronic lumbar degenerative pain after complex rehabilitation treatments

This study is a continuation of the previous ones, in which we wanted to evaluate the evolution of pain of patients and of the quality of their life after the rehabilitation treatments.

The analog visual VAS scale is frequently used in the quantification of pain, including chronic pain, and there are many studies on chronic low back pain that have used this scale, due to the fact that it is very easy to apply to patients. It has been frequently used in patients who have performed various programmes / exercises / forms of movement [40], [41], [42], [43], [44], [45], [46], [47], [48]; or on therapies with physical factors [49], [50], [51], but fewer studies. In our study, the VAS scale decreased the initial values, after the treatments performed, in all patients in the study, regardless of the group, and the differences were statistically significant (Figure 7), which continues the trend published on a group of patients who were part of the group that performed cold mud baths [7], or the one in which there were analysed 2 groups of patients - cold baths and the control group - where the values decreased in both groups of patients [52].

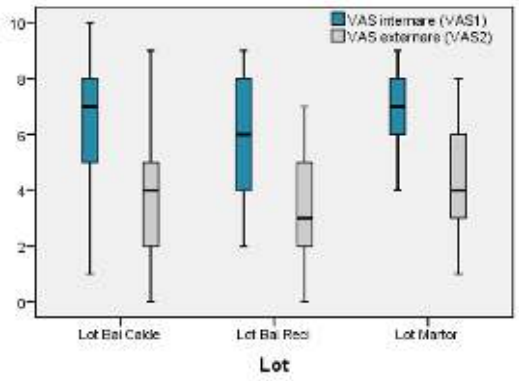

Figure 7 - Box-Plot graphical representation of VAS values for each study group

Warm mud therapy determines a decrease of 3,498 times higher of pain than cold mud therapy. Age does not influence pain; no significant difference was observed regarding the values recorded at the two age categories, all patients registering lower values at discharge than at admission, which was true for both sexes. All patients, regardless of their weight, had a statistically significant decrease in pain on this scale.

The pain catastrophizing scale (SCD) is not commonly used to monitor chronic low back pain, as it has both organic and psychological triggers [53], [54], [55]. In our study the SCD scale had lower values at discharge than at admission, and the differences were statistically significant for all patients in the study, regardless of group (Figure 8). Both mud therapies determined in equal way the reduction of values at discharge of the scale. Patients over the age of 50 had slightly higher values than younger patients, both at admission and discharge, and the values at discharge were statistically significant in patients over 50 years old. Female patients

had higher values than male patients, and discharge values decreased in both sexes, with statistically significant differences. It was observed that overweight patients had higher scale values at admission and discharge, and only overweight patients showed statistically significant differences at discharge.

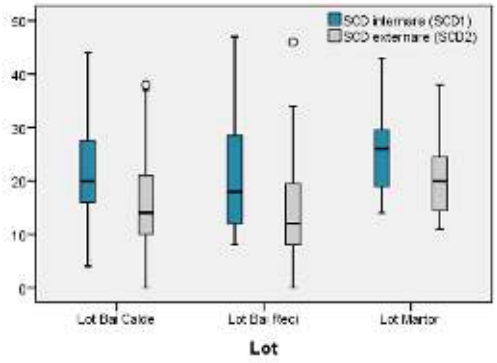

Figure 8 – Box-Plot graphical representation of SCD values for each group of patients

The analysis of patients' quality of life is important due to the fact that pain is closely related to organic factors but also to psychological factors. **The SF-36 questionnaire** is frequently used not only in research on chronic low back pain [56], [57], [58], but also in various programmes aimed to reduce low back pain [59], [60].

In our study, all sections of the questionnaire recorded an improvement in values, statistically significant ($p < 0.05$), after treatment, in all groups under observation, but in the control group 4 sections (Vitality, Mental Health, Social Function, General Health) the differences recorded, although at discharge the values were higher than at admission, were not statistically significant. We consider that this is also due to the fact that the number of patients in the control group was lower compared to the number of the other two groups, and we believe that in the future we can increase the control group to better quantify the quality of life of patients with this common disease.

4. General conclusions

Conclusions regarding the general characteristics of the patients from the studied groups

- The average age of the patients in our study was 56.5 years.
- More than half of the patients were females.
- Overweight and obesity is a characteristic of the patients in our study.
- Patients from urban areas are mainly referred for hospitalization rehabilitation treatments.

- Patients with a low level of education rarely seek medical advice from a rehabilitation doctor.
- The onset of low back pain often coincides with a low back strain.
- The vast majority of patients in the study have a history of low back pain for more than 5 years.
- Married patients who are still in work, but sedentary, are those who require rehabilitation treatments to reduce pain.
- Patients with chronic low back pain frequently use medication treatments to relieve pain.
- Patients with lumbar degenerative pathology undergo rehabilitation treatments in hospitalization annually.
- Amongst the degenerative pathologies, the most common in our study was Lumbar Spondylosis

Conclusions on the evolution of disability in the patients in study 1

- Mud treatments decrease the disability of patients with chronic low back pain. Warm peloidotherapy influences mostly the disability quantified by the Roland Morris questionnaire, while the Quebec disability scale and the Oswestry disability index are equally influenced by mud therapies.
- Patients appreciate disability differently, those over the age of 50 face a higher degree of disability than younger patients, and although there have been significant improvements in both age groups, elderly patients have had notable results in discharge after rehabilitation treatments.
- Females reported a higher degree of disability than males, but both sexes had favorable outcomes after treatment (one exception recorded on the Quebec scale for females).
- Disability is more common in overweight and obese patients than in normal-weight patients, but in both categories of patients the disability has improved significantly after rehabilitation treatments.
- Rehabilitation treatments (with and without natural factor) decrease the degree of disability of patients with chronic degenerative low back pain.

Conclusions on the evolution of lumbar spine mobility in the patients in study 1

- Peloido-therapy with cold bath applications determine a more significant improvement in mobility, quantified by the Back Performance Scale, compared to hot mud baths, but both mud therapies bring significant benefits to lumbar spine mobility.
- Patients over 50 years of age have a lower degree of mobility compared to younger patients, but both age categories increased their lumbar spine mobility after the complex recovery treatment, but the category where there was a statistically significant increase was that of elderly patients.
- Patients, regardless of sex and weight, gained in degrees of mobility at the end of the treatment course, the differences were significant for all categories of patients in the 3 groups, mobility quantified by scales and specific indices.

Conclusions on the evolution of serum serotonin in the patients in study 2

- Treatments with hot mud baths increase serotonin values to a higher degree compared with treatments with cold mud baths.
- As we get older, our serum serotonin levels will decrease.
- Women have slightly higher serotonin values compared to men.
- Overweight and obesity decrease serotonin levels.
- Serotonin was increased in all patients in the study regardless of gender, age or weight after a rehabilitation treatment regimen, even without a natural factor.

Conclusions on serum evolution of brain-derived neurotrophic factor (BDNF) in the patients in study 2

- Rehabilitation treatments without natural factor, hydro-kineto-therapy and kineto-therapy decrease the values of serum BDNF.
- Young patients have higher serum BDNF values compared to elderly patients **.**
- Women have slightly higher serum BDNF values compared to men
- Overweight and obesity are a factor that causes a decrease in serum BDNF values
- Complex rehabilitation treatments with peloido-therapy, hydrokinetotherapy and kinetotherapy increase serum BDNF levels, regardless of gender, weight, or age.

Conclusions on the evolution of pain and quality of life of the patients in study 3

• Rehabilitation treatments, both those with natural factor and those without natural factor reduce the pain in patients with chronic degenerative pathology of the lumbar spine

- Warm mud baths influence the degree of pain felt by the patient (by decreasing it), more than cold mud baths as it is shown by the visual analog scale VAS
- Pain, quantified by The Pain Catastrophizing Scale, is similarly influenced by the two mud therapies, both of which reduce pain.
- With age, pain is perceived differently, especially on The Pain Catastrophizing Scale, where elderly patients have higher values compared to younger patients.
- Women quantified pain as more catastrophic compared to men, the same was observed in overweight or obese patients compared to normal–weight patients.
- Patients' quality of life has been improved after complex rehabilitation treatments.

Final conclusions

- The addressability of patients who visit a physician for lumbar degenerative pathology, in order to undergo rehabilitation treatments differ in sex, age and educational level.
- Elderly, overweight or obese patients have a higher degree of pain, disability, lower mobility of the lumbar spine and lower serum levels of serotonin and BDNF, compared to younger and normal-weight patients.
- Recovery treatments, especially those with natural factor, together with hydro-kineto-therapy and kineto-therapy therapies bring significant benefits to the patient with chronic degenerative lumbar pain causing: decreased disability, improved mobility, decreased pain, increased serotonin and BDNF serum and improving the quality of life.

5. The originality of the thesis

The original element of this research is the use of two serum parameters - serotonin and brain-derived neurotrophic factor - which are closely related to chronic pain, which have not been studied in patients who had complex treatments of balneo-physio-hydro-kinetotherapy. The two serum markers were evaluated dynamically, before and after the treatments, having the results compared within the 3 groups. We consider that the study performed is an important step in quantifying pain by both clinical and especially serological parameters. We want to be able to continue the research, by using more patient groups, and further on to be able to quantify serum at longer intervals.

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