

Analyze the role of environmental and immunological factors in degenerative and inflammatory rheumatological disorders

PhD thesis

Edit Vereckei

Clinical Medicine Doctoral School

Semmelweis University



Supervisor: Dr. Klára Törő MD, PhD.

Official reviewers:

Dr. Judit Várkony MD, Ph.D.

Dr. Márta Péntek MD, Ph.D.

Head of the Final Examination Committee:

Dr. Judit Demeter MD, D.Sc.

Members of the Final Examination Committee:

Dr. Margit Szentesi MD, Ph.D.

Dr. Katalin Borka MD, Ph.D.

Budapest, 2012

1. INTRODUCTION

Genetic susceptibility, external factors such as psychological components and infections play a role in the manifestation of almost all locomotor disorder groups according to our present knowledge.

Low back pain is one of the most common locomotor syndromes that makes patients to seek medical help. During active lifetime 60% to 85% of people have some kind of back pain. The importance of minor repeating or a single major physical strain in the development of symptoms is undoubted. Both activity-arm lifestyle, sitting in front of the computer and injuries to the spine during physical activity and posture and during work may play all a role in the development of the complaints. However, the role of psychologic stress is not negligible in the development of back pain.

One of the most common disorder that may be related to working activity and conditions is back pain due to its developmental mechanisms where these factors contribute to the development and progress of this multifactoral disease. Disorders that may be related to working conditions should be differentiated from occupational diseases where the exclusive causative relationship between occupation, strain at workplace and the development of the disease is the diagnostic criteria. This is one of the most difficult tasks in case of back pain.

If it becomes necessary to clarify the underlying cause of persisting or progressing back pain with imaging studies it is not rare that not only a series of degenerative lesions are detected but also unexpected opinion will be given that urges the confirmation or rejection of the diagnosis raised by radiology. This is the case if spondylodiscitis is raised by the radiologist while discopathy was suspected. Besides degeneration of the disc as one of the degenerative lesions of the spine the osteoarthritis of small joints is the process that predisposes the development of subluxation of small joints due to the thinning of the cartilage. It results in symptoms of segmental instability (anterolisthesis, retrolisthesis and laterolisthesis, summarized as pseudolisthesis). That is well-known in X-ray as well. The same can be observed with MRI as Modic sign a thin striped reaction in the vicinity of the disc. Metabolic bone diseases and inflammatory lesions may also cause back pain. In celiac disease metabolic osteopathy often occurs. In the development of osteoporosis abnormal absorption of calcium plays an essential role. This mechanism leads to osteoporosis, osteomalacia and secondary hyperparathyreosis in celiac disease affecting the small intestines. Other locomotor symptoms that are present in celiac disease were described by Adelazzi et al in 1982. Later Bourne et al reported cases of

gluten sensitive enteropathy where arthritis was the leading symptom including inflammatory abnormalities of the sacroiliac joint.

Therapy is practically an environmental factor with which we intend to positively influence the disease. Therapies can be judged how the effectiveness and the accompanying risk are, thus, what the realistically expected adverse reactions of the specific therapy are, how severe they are and how often they occur. There are traditional methods among the therapeutic possibilities such as balneotherapy and modern modalities such as biological therapies of certain inflammatory and autoimmune diseases. The expected benefit and risk of the above-mentioned therapies is certainly not equal.

2. AIMS

2.1 Analysis of environmental factors causing chronic back pain

Analysis of factors impairing the successful treatment of patients suffering from chronic, non-specific back pain that do not improve despite complex therapies, sometimes successful or repeated operations due to disc herniation with special emphasis on psychological components.

2.2 Analysis of findings of imaging studies performed in patients with chronic back pain

Analysis of cases of patients with progressing pain of the lumbar spine and where the finding of the imaging study raised the suspicion of spondylodiscitis. Based on the available clinical data – analysis of the X-ray images and other imaging studies together with a radiologist – setting up the right diagnosis.

2.3 Validation of the GALS evaluating method in Hungary and its use in occupational hygiene among miners

Validation of GALS evaluating method in healthy population and patients. Locomotor screening of healthy miners in respect of occupational hygiene with the validated evaluating method.

2.4 Evaluation of the role of environmental and psycho-social factors in the health condition of Hungarian miners – with special respect to locomotor abnormalities

Evaluation and analysis of the relationship of patient groups concerning environmental, psycho-social factors, locomotor complaints and public health and evaluation of occupational, socio-demographic and psychological factors causing locomotor complaints referring to occupational hygiene among able-bodied workers.

2.5 Locomotor abnormalities in gluten-sensitive enteropathy with special emphasis on analysis of causative factors of back pain

Horizontal and longitudinal evaluation of locomotor abnormalities in a population with celiac disease based on the clinical, laboratory and radiological findings.

2.6 Therapeutic risk-benefit analysis of different rheumatologic disorders – the positive and negative effects of therapy, drug adverse reaction as health impairing environmental factor

2.6.1 Analysis of rare adverse reactions during TNF-alpha-inhibitor therapy with reference to a case report.

2.6.2 Confirmation of the efficacy of balneotherapy in the setting of a prospective, controlled trial in a patient group with back pain.

3. **METHODS**

The trials described in the followings were implemented in different designs that were always customized according to the study goals. The relationship between environmental and psychosocial factors and locomotor complaints and disorders were analyzed in case-control, cross-sectional evaluations focusing on a target group with high risk (miners) with respect of locomotor disorders. The possible application and the outcomes of the evaluating tool (GALS questionnaire) made for screening are presented based on a sample from an occupational target group with high risk.

3.1 Methods used for the analysis of environmental factors causing back pain and for the evaluation of environmental and psycho-social factors affecting the general health condition especially the locomotor abnormalities of Hungarian miners

Patients: 102 patients with back pain and 199 healthy people matched on age and sex were enrolled. The latter ones were chosen from the database of Hungarostudy-2006 a representative population health survey. In the other study 177 miners took part who were active workers.

Methods: the SF-36 questionnaire validated also in Hungary was used for evaluating quality of life, while the short version with 9 items of Beck Depression Inventory (BDI) and the General Well-being Index (WBI-5) and the anxiety subscale with 7 items of the Hospital Anxiety and Depression Scale (HAS) were implemented for characterizing the psychological condition.

3.2 Methods used for analyzing the findings of imaging studies in patients with chronic back pain

Patients: 10 patients suffering from progressing chronic back pain were enrolled in whom MRI raised the suspicion of spondylodiscitis.

Methods: parameters measuring inflammatory activity (Erythrocyte sedimentation rate, blood count, C-Reactive Protein) and confirming infection (antistreptolysin test, liver function test, alkaline phosphatase) were chosen from laboratory tests.

Besides MRI the following imaging studies were used: detailed radiologic analysis with standard X-ray, CT, isotope bone scan with technetium and gallium.

3.3 Use of GALS physical examination method for complex locomotor screening of Hungarian miners

Patients: 148 miners who were active workers were screened for locomotor disorders in 4 mines (Mines in Bükkábrány and Visonta of Mátra Power Station Share Company and Mine in Márkushegy of Vértes Power Station) with the help of occupational hygiene services.

Methods: GALS evaluating method validated in Hungary.

3.4 Analysis of factors causing locomotors lesions in gluten-sensitive enteropathy, principally back pain

Patients: 21 with gluten-sensitive enteropathy took part voluntarily in the study between 1994 and 2005.

Methods to detect sacroiliac abnormalities

Clinical, laboratory and complex radiological methods were combined.

Laboratory examinations: erythrocyte sedimentation rate and CRP to measure inflammatory activity, protein electrophoresis (to exclude myeloma).

Imaging studies: anteroposterior and lateral image of the lumbosacral joint and detailed radiologic analysis with standard X-ray of the sacroiliac joint, isotope bone scan with technetium-99m-pertechnate, high-resolution CT (HRCT) and MRI of the sacroiliac region.

Methods to detect osteometabolic abnormalities

Following examinations were carried out in the patient group described above:

Laboratory examinations: blood calcium, phosphor, alkaline phosphatase, analysis of the calcium content of the 24-hour and the first morning urine, blood vitamin D3 and parathormone.

Imaging studies: detailed radiologic analysis with standard X-ray and osteodensitometry of the lumbar region and the left hip.

Design of the study: cross-sectional and longitudinal analysis.

3.5 Methods used for therapeutic risk-benefit analysis in different locomotor disorders

3.5.1 Method used for therapeutic risk-benefit analysis of TNF-alpha-inhibitor therapy in rheumatoid arthritis

Case report of a patient with rheumatoid arthritis receiving TNF-alpha-inhibitor therapy

3.5.2 Methods used for evaluation of the efficacy of balneotherapy in patients with chronic back pain

Patients: the study was conducted in 3 different factories in Budapest. In the survey 2541 subjects doing light physical work took part. All together 845 agreed to have a rheumatological examination, 371 patients has back pain, 170 were randomized.

Methods: the 3 inclusion criteria are (a) back pain localized to the lumbosacral region not radiating into the leg; (b) pain lasting for at least 1 and maximum 3 month before the enrollment; (c) back pain for years before the present episode.

Into 4 groups 170 patients were randomized in the study. Group A received balneotherapy, group B underwater massage (tangentor), group C weightbath hydrotraction and group D was allowed to take only NSAID and they were the control group. Patients were treated after work for 1 month. Every treatment took place in the same hospital in water of 37 °C for 15 minutes 3 times a week for 4 weeks. Every patient could strain its spine as usual.

Every patient was evaluated according to the set standpoints at entering the study, 4 weeks and 1 year later respectively.

Following characteristics were assessed at every examination:

- (a) pain score on 0 to 100 mm visual analogue scale.
- (b) number of analgesic tablets (NSAID) within 24 hours before the assessment.
- (c) angle of lifting the straight leg (Lasegue's sign) measured with goniometer on both legs.
- (d) measurement of flexion, extension and lateralflexion of lumbar spine with goniometer.

The physician performing the assessment did not know the therapeutic randomization.

4. RESULTS

4.1 Results of the analysis of environmental factors causing chronic back pain

Data of 102 patients were evaluated with the methods detailed in section 3.1. Seventeen male and 85 female patients were involved. The mean age of patients was 57.8 years (SD=12.8). Patients enrolled in the study suffered from non-specific chronic back pain and received a complex balneo-physiotherapy that did not alleviate their pain. Since the operation due to disc herniation or in case of repeated surgeries since the last operation at least 1 year has passed. None of the subjects had a history of known, treated depression.

In the patient population 2 individuals had not and 8 had completed elementary school, 24 people graduated from trade school, 20 from vocational secondary school, 18 had A-level and 20 university degree.

Concerning the marital status 13 subjects were divorced, 61 married, 2 patients married but living separated, 8 patients single and 18 patients were widows.

The mean value of HAS referring to the severity of anxiety and characterizing the patient group was 7.9 (SD=4.75) that is a borderline value between normal and abnormal conditions. There was a significant difference ($p<0.0001$) between the mean HAS values in the patient and the control group.

The short Hungarian version of the WHO Well-being scale with 5 items was used. The mean WBI-5 scale was 15.7 (SD=5.4) in patients and 8 (DS=3.9218) in the control group. The difference between the results of the WHO Well-being scale in the control and the patient group was significant ($p<0.0001$).

Based on the Beck scale values the distribution in the patient group was following: 51% were within normal range, 21.6% proved to have mild, 15.7% moderate and 11.8% severe depression.

The relationship of normal, mildly, moderately and severely depressed groups based on the Beck scale was evaluated in patients who had one, two or several operations of the spine or who had no operation at all.

Almost half of the patients (49%) with back pain suffered from mild, moderate or severe depression. Forty patients from subjects with back pain had no history of spinal operation and did not suffer from depression. Half of the patients (9 subjects) with 1 surgery had depression, while 5 patients from those who had several operations (8 subjects) proved to suffer from depression. Thirty-six patients had depression out of 76 (47.4%). There is a relationship between depression and spinal surgery the contingency coefficient is 0.211. There was no significant difference between the Beck scale outcomes of patients with different educational level ($p=0.09$) and different marital status ($p=0.70$).

The BDI values of patients and the population-based control group were compared: the mean BDI was 9.5 in patients and 4.4 in the population-based control group. The difference is significant ($p<0.0001$) between the examined patient group and the population-based control group.

One percent of patients with back pain was undernourished, 20.6% had normal BMI, 27.5% was overweight, 14.7% was severely overweight and 36.3% was obese.

The body mass index of the patient and the control group was compared. The mean BMI value of patients was 28.6 (SD=6.2) and of the population-based control group 25.5 (SD=4.4). The difference of BMI in patients and the general population was significant (($p < 0.0001$)).

We analyzed whether there is a relationship between the body mass index (BMI) and the spinal operation or the number of operations. The contingency coefficient is 0.2554, thus, there is a relationship indeed.

Forty-eight percent of patients had hypertension, while 8.8 % had diabetes. Gastrointestinal disorders occurred at a rate of 9.8%. There was a significant difference between patients with different BMI in respect of hypertension, diabetes and gastrointestinal disorders (in hypertension $p = 0.0001$, in diabetes $p = 0.0158$, in gastrointestinal diseases $p = 0.0149$). Thus, there are more patients with higher BMI who suffer from cardiovascular, metabolic or gastrointestinal co-morbidities as well.

There was no statistical relationship between depressing mood and the disorder groups above. There was no significant difference regarding the SF-36 dimensions in the groups of different age group, educational level, marital status, type of work and number of working years among patient with or without locomotor complaints.

4.2 Results obtained from the revision of imaging studies in patients with low back pain

The method discussed under section 3.2 was used to examine 9 female and 1 male patients with suspected spondylodiscitis. Their mean age was 61.1 years (39-78). After the assessment of the results and the repeated overview of MRI images the cases included in the study can be grouped as follows:

1. Infectious spondylodiscitis was clearly verified in 4 cases. In the past medical history of these patients there is a definitive event when the infectious agent could have entered the body.
2. The diagnosis proved to be inconclusive in 2 cases where a presently inactive process was revealed and the results were not fully in accordance with the clinical findings. Thus, this may indicate future revision of the current diagnoses.
3. Spondylodiscitis was explicitly excluded in 4 cases. It was the Modic sign in the MRI images that caused diagnostic problems in these cases.

The evaluation of the findings of imaging studies was performed in compliance with international standards.

4.3 Results obtained from the GALS physical examination method in complex locomotor screening of Hungarian miners

148 men were screened with the methods discussed under section 3.3. The screening revealed locomotor involvement in 87 individuals (57%) the mean age of this group was 41 years (24-56). Sixty-four individuals (43%) were healthy concerning their locomotor condition and their average age was 37 years (22-54). Analysis of the relationship of objectively detected abnormalities, the type of work, age and time of employment revealed that there is a higher rate of people with objective abnormalities among people who performed light physical work, were older and had a longer time of employment. A wide range of locomotor abnormalities was observed from insignificant ones to severe (temporary) locomotor disabilities.

4.4 Results obtained from the assessment of environmental and psycho-social factors affecting the general health condition of Hungarian miners with special emphasis on locomotor abnormalities

The methods discussed under section 3.4 were applied to examine 177 miners. The mean age of the examined individuals was 44.8 years (28-60 years, SD=8.02). More than half of the study cohort (55%) performed moderately heavy, 39% heavy physical work, whereas only 6% performed light physical work or administrative duties.

Most of them (63%) were skilled workers, one third of the cohort had A-level or tertiary qualifications (33%). The ratio of those living in relationship exceeded 80%. The average of the years of employment was 25.2 (SD=8.4). The examined individuals had a minimum of 10 years of work experience, the maximum years of employment was 42 years. All individuals were economically active at the time of the study. Eighty-one of 177 miners (46%) reported current locomotor complaints. Seventy-six percent of the affected individuals had spinal complaints, 42% and 10% of them had large joint pain and small joint pain, respectively. As for the type of the experienced pain, most of the affected individuals (67%) reported one type, approximately a quarter of them (27%) two types and 6% of them three types.

Apart from locomotor complaints the assessment of the condition included the incidence of other disorders and of previous operations as well. More than a quarter of the inquired individuals (27.7%) were diagnosed with at least one disorder and the ratio of those with a medical history of previous operation was approximately the same (27.2%). Hypertension was registered nearly in one fifth of the cohort (19%) the incidence of diabetes and gastrointestinal disorders exceeded 5%.

In addition to body symptoms, complaints and disorders we also evaluated the miners' BMI values and health-related quality of life. The average BMI value was 27.86

(SD=3.74) that lies in the obese range. The mental condition as a characteristic feature of health-related quality of life was evaluated with the shortened Beck Depression Inventory. Scores showed that more than three-quarters of the individuals (73%) belonged to the normal, slightly more than one tenth (13%) to the mild, 10% to the moderate range and 2% to the range described as severe clinical depression.

The average WHO Well-being Inventory was 9.3 (SD=5.3), the average value of the anxiety scale (HAS) was 4.5 (SD=3.3).

According to the dimensions of the SF-36 questionnaire the examined miners assessed their physical and social conditions as the most favorable feature, i.e. they evaluated their performance higher than 80 percent. In contrast, the evaluation of physical pain and general medical condition was only slightly higher than 60 %. Subjects belonging to the normal, mild or moderate range in the Beck Depression Inventory showed significant deviations in all SF-36 dimensions, i.e. health-related quality of life factors of individuals in the higher depression ranges were respectively worse.

Furthermore, the type of relationship of the occurrence of locomotor complaints that has a very high incidence among miners with the socio-demographic factors (age, level of education, marital status), the variables regarding work performance (type of work, years of employment), incidence of specific disorders, physique (BMI) and factors of health-related quality of life such as depression or mental wellbeing was evaluated.

Five factors showed significant relation to the incidence of locomotor complaints: age, years of employment, the incidence of two co-morbidities, hypertension, gastrointestinal disorders and weight. Individuals with locomotor complaints are approximately 3 years older and have been employed for 3 years longer than the average. More than a quarter of them (28%) had the diagnosis of hypertension, while in individuals with no locomotor complaints only 10% of miners were affected by it. Gastrointestinal disorders occurred exclusively in individuals with locomotor complaints with a ratio of 12%. Physique was characterized by the Body Mass Index. Although the mean BMI of both groups exceeded normal values and were in the obese range, this value in the locomotor group was even higher. Since the correlation between age and years of employment proved to be significantly high ($R=0.88$), only one of the variables was included in our regression model. According to the parameters of the above model significant correlation was only seen between hypertension and locomotor disorders which means that the probability of locomotor disorder is 2.5 times higher in miners with hypertension than without.

4.5 Results of the evaluation of locomotor abnormalities – analyzing mainly sacroiliac and osteometabolic abnormalities – associated with gluten-sensitive enteropathy. Cross-sectional analysis of clinical, laboratory and radiological findings in 21 patients

The methods discussed in section 3.5 were used to examine 21 patients. The patient group comprised 19 female and 2 male patients, the mean age was 45.7 years (26-68). None of the patients reported spontaneously low back pain. On questioning 15 patients (71%) mentioned back pain. None of the patients reported sciatic pain or pain typical for sacroiliitis. Only one patient reported nocturnal pain.

Data of 21 patients included in the cross-section analysis were evaluated.

None of the patients took regularly corticosteroid or non-steroid anti-inflammatory drug only occasional paracetamol usage was reported. Seven patients (33%) reported peripheral arthralgia. On physical examination of the sacroiliac joint the Mennel sign was often positive, but it is not a specific sign in itself. Signs indicating radicular involvement were not observed. Results of the laboratory tests revealed low inflammatory activity. Increased erythrocyte sedimentation rate with moderate hypergammaglobulinemia was detected in 7 cases (33%). No other significant laboratory deviations were found. Conspicuous sacroiliitis was observed in 2 patients (9.5%). MRI and HRCT detected synovial fluid, constrictions, irregularities, erosions, sclerosis and the calcification of intraarticular ligaments.

Longitudinal analysis of clinical, laboratory and radiological findings of a follow-up study in 8 patients

Eight patients on gluten-free diet participated in a 11-year-long follow-up study between 1994 and 2005. Their mean age in 1994 was 46.7 years (42-56), the average duration of disease in 2005 was 23 years (11-42). After 11 years of follow-up all 8 patients had back pain and 5 of them reported permanent pain.

Analysis of the involvement of the sacroiliac joint and comparisons of X-ray images of 1994 to those made in 2005 progression was observed in 2 patients. Based on the isotope bone and MRI scans 50% of the patients had active sacroiliitis at the time of the examinations. HRCT revealed the definitive morphologic progression of the sacroiliac joint-involvement. Sacroiliac joint abnormalities were detected in 5 patients (62%) in 1994 and in 8 patients (100%) in 2005. Sacroiliac ankylosis did not occur in any patient despite the 23-year average duration of the disease.

Results of the evaluations performed to assess changes in osteometabolism

Osteometabolism test results of the 21 patients included in the cross-sectional study

Radiological findings did not reveal vertebral compression fractures in the lumbar region, however, in 13 cases signs of decalcification and an arcing pattern of the lamellar structure suggestive of osteoporosis were observed. Osteodensitometry revealed density values suggestive of osteoporosis in 4 patients, of osteopenia in 6 patients, while 11 patients had normal density values. In 3 patients decreased blood calcium levels and in 8 patients decreased 24-hour urine calcium output values were observed. Elevated alkaline phosphatase levels were found in 4 cases. In 11 patients decreased vitamin D levels, in 4 patients elevated blood parathormone levels were registered. Characteristic laboratory value deviations included decreased vitamin D-25OH and blood calcium levels and elevated alkaline phosphatase and blood parathormone levels.

Osteometabolism test results of the 8 patients included in the longitudinal follow-up study

In 2005 T-score values suggestive of osteoporosis, osteopenia and normal functions were registered in 5, 1 and 2 patients out of the 8 examined patients, respectively. The following additional laboratory value deviations were registered: decreased vitamin-D3 levels in 5 patients, decreased blood calcium levels in 1 patient, elevated alkaline phosphatase levels in 2 patients and elevated blood parathormone levels in 3 patients were registered. In 2005 two patients had a bone density in osteoporosis and osteopenia range and decreased level of vitamin D3 and in two patients newly-recognized elevated blood parathormone levels were found compared with values in 1994. The possibility of bone density loss with postmenopausal origin according to the mean age of 57.75 (52-67) of the examined women should certainly be considered as well.

4.6 Results obtained from evaluating the therapy – as an environmental factor – of rheumatological disorders of different severity and pathomechanism

4.6.1 Adverse reactions during administration of anti-TNF-alpha therapy

The 53-year-old patient in the case report that was constructed following the method discussed in section 3.6.1 had a past medical history of deep vein thrombosis of the lower limb and resulting pulmonary embolism in 1987. The patient was anticardiolipin negative at that time. She received anticoagulant therapy for 6 months. She was diagnosed with rheumatoid arthritis in 2002. As first-line therapy methotrexate (MTX) was initiated and then since 2005 the patient was on MTX-leflunomide combination therapy due to her persisting activity symptoms. She received small-dose oral steroids since the onset of her condition. Considering the persisting activity anti-TNF-alpha therapy was initiated in November 2006. Infliximab was administered in a 3mg/kg dose. The patient's DAS28

value was 6.01 at that time the immunoserological results were negative for anti-DNS and aCL antibodies.

The activated PTT time was within normal range, lupus anticoagulant results were negative. Other commonly known causes of thrombophilia were excluded. In 2007 after the third infliximab infusion the DAS28 value dropped to 3.1, but simultaneously IgM-type aCL antibodies appeared in high titers. A month later the patient developed soft tissue infection of the heel and initially Streptococcus, later Staphylococcus could be cultured from the wound discharge. The patient received local antiseptic and continuous systemic antibiotic treatment. Infliximab administration was suspended along with the MTX and leflunomide administration because of the persistent soft tissue infection unresponsive to therapy. Immunoserology showed persisting high titers of IgM-type aCL antibodies that were controlled every 12 weeks.

In November 2007 necrotising vasculitis developed on the toes and dominantly on one finger. ANCA and cryoglobulin could not be detected, virus serology results were negative. In January 2008 the patient developed deep vein thrombosis of the lower limb despite preventive LMWH therapy, so we initiated LMWH in therapeutic dose and put the patient on continuous coumarin therapy afterwards. Methyl-prednisolone pulse therapy was applied, but proved to be unsuccessful so we performed plasmapheresis and the patient received human intravenous immunoglobulin in 0.4 g/kg dose and cyclophosphamide repeatedly. The clinical symptoms regressed the patient became anticardiolipin-negative the soft tissue infection was protracted but finally regressed.

4.6.2 Results of prospective, controlled balneotherapy in patients with low back pain

In the framework of the study conducted according to the methods discussed in section 3.6.2, 158 patients underwent balneotherapy, which was basically well tolerated by every patient. The control group consisted of 53 patients who did not receive therapy. Directly after balneotherapy the analgesic drug consumption significantly decreased ($p < 0.01$) in the treatment group whereas the same could not be applied to the control group. There was no significant difference at any time in the analgesic drug consumption of the 3 treatment groups. The results were similar when evaluating the pain scale. After 1 month of therapy the pain relief was significant ($p < 0.01$) in all treatment groups. Pain relief was also reported in the control group, but it was not significant. There were no significant changes – compared to initial results – in the range of spinal movements and the straight leg raise test results after 1 month of therapy, although, most patients considered it efficient. One year later we could make appointments for follow-up with 158 out of 170

patients. The majority thought their low back was in better condition than it had been at the time of the first examination and there was no difference of opinion in the 3 groups. However, the number of analgesic pills consumed daily was dramatically reduced among treated individuals and the same was true 1 year later at the time of the follow-up consultation($p<0.01$). There was no reduction of analgesic usage in the control group patients.

5. CONCLUSIONS – NEW STATEMENTS

1. It was established that one of the factors impairing the efficient treatment of patients not satisfactorily responsive to complex therapy is depression that affects 49 % of the examined patients. There is a significant difference between the examined patient group and the population-based control group with respect to the BDI ($p<0.0001$). Twenty-five percent of the examined patients had operation due to herniated disc, 54 % of them were diagnosed with depression of varying severity. The incidence of depression among patients with one and those with multiple operations was 50% and 62.6%, respectively.

There is definitely a connection between depression and spinal surgery. Currently, there is no other study in the literature that analyzes depression as a contributing factor to chronic low back pain due to one or multiple disc hernia surgeries in the patient population.

2. We analyzed the case reports and results of imaging studies of ten patients with progressive lumbar pain where imaging studies raised the possibility of spondylodiscitis. Infectious spondylodiscitis could be verified only in 4 cases after reevaluating clinical data and the findings of imaging studies. The diagnosis was found to be inconclusive in 2 cases, while in 4 cases spondylodiscitis could be unambiguously excluded. In these cases only Modic signs could be detected in the MRI images that caused the diagnostic problem. In 2005 we were the first in Hungary to analyze this problem from rheumatologic aspect. Prior to that there had been two scientific reports published on the differential diagnostic problem of the two abnormalities in the MRI images and discussing the matter from a radiologic point of view. One was published in *Neuroradiology* in 2004 and the other article was published in *LAM (Mester)* in 2000.

3. We validated the GALS method in Hungary. We concluded that it is suitable for locomotor screening. Using this method we detected the presence of objective locomotor abnormalities in 57 % of active miners who had previously been declared healthy by occupational health measures.

4. Based on the evaluation of environmental and psycho-social factors, locomotor complaints and disorders with public health relevance we concluded that the incidence of locomotor complaints in miners was strongly related to 5 factors, namely to age, years of employment, the incidence of hypertension and gastrointestinal disorders and to physique.

5. Based on the analysis of factors causing locomotor abnormalities (with particular interest to low back pain) associated with gluten-sensitive enteropathy we found that in gastrointestinally asymptomatic patients on gluten-free diet HRCT was the method that revealed the definitive morphologic progression of the sacroiliac joint-involvement, i.e. the subclinical sacroiliitis, although patients did not experience significant inflammatory low back pain. We were first to conduct a longitudinal study with respect to sacroiliac joint lesions and we verified that 62% of sacroiliac abnormalities could be detected in 1994 and that the ratio was 100% after 11 years in 2005.

6. We analyzed the positive and negative effects of the treatment of rheumatologic disorders.

6.1 We concluded and were one of the first to report that in a patient with rheumatoid arthritis following good response to infliximab therapy a fairly rare side effect developed: secondary antiphospholipid syndrome and necrotizing vasculitis occurred simultaneously with positive IgM-aCL results. The accompanying infection and the consecutive sudden termination of anti-TNF-alpha therapy may have played a role as well.

6.2 We concluded based on the prospective, randomized, controlled trial in patient groups with low back pain that different types of balneotherapy applied as monotherapy are effective and basically well tolerated. In the short term balneotherapy promotes pain relief, its long term application results in lower analgesic consumption.

LIST OF OWN PUBLICATIONS

First-author publications related to the thesis

Articles in journals

1. **Vereckei E**, Kriván G, Reti M, Szodoray P, Poor G, Kiss E (2010) Anti-TNF alfa induced antiphospholipid syndrome manifested as necrotising vasculitis. Scand J Rheumatol,39:175-177 **IF : 2.594**

2. **Vereckei E**, Mester A, Hodinka L, Temesvári P, Kiss E, Poor G. (2010) Back pain and sacroiliitis in long-standing adult celiac disease: a cross-sectional and follow-up study Rheumatol Int,30:455-460. **IF 1.431**

3. **Vereckei E**, Szodoray P, Poor G, Kiss E.(2011) Genetic and immunological processes in the pathomechanism of gluten-sensitive enteropathy and associated metabolic bone disorders. *Autoimmun Rev*, 10:336-340. **IF: 6.556**
4. **Vereckei E**, Temesvári I P, Juhász P, Palkonyai É, (2005) Derékfájás a járóbetegellátás szemszögéből. [Lower back pain from outpatient care aspect] *Praxis*, 14:33-40.
5. **Vereckei E**, Palkonyai É, Simoncsics E ,Polgár A, Temesvári P.(2007)Alsóvégtagi derékfájdalmak gyakorlatias szemlélete. [Practical view of back pain radiating into the lower limbs] *Praxis*, 11: 849-858.
6. **Vereckei E**, Palkonyai É,Simoncsics E, Polgár A, Temesvári IP. (2009) Alsó végtagi fájdalmak. [Lower limb pain] *Studium&Practicum*, 3:10-13.
7. **Vereckei E**, Weis M, László A, Bély M, Banai J, Korondi I.(1993) Ritka bélbetegség mozgásszervi megnyilvánulásai. [Locomotor manifestations of a rare bowel disease] *Magyar Reumatol*, 34: 403-406.
8. **Vereckei E**, Mester Á, Király M,Palkonyai É, Juhász P, Kaposi NP, Temesvári IP.(2005) A spondylodiscitis terminológiájáról és differenciáldiagnosztikájáról néhány eset kapcsán [About the terminology and differential diagnosis of spondylodiscitis with reference to some cases] *Osteológiai közlemények*, 13:139-145.
9. **Vereckei E**, Mester Á, Hodinka L, Temesvári IP.(2007) Glutenszenzitív enteropathiás betegek gyulladásos mozgásszervi eltéréseinek és csontmetabolizmusának vizsgálata. [Evaluation of inflammatory locomotor lesions and osteometabolism in patients with gluten-sensitive enteropathy] *Magyar Reumatol*, 47:31-41.
10. **Vereckei E**, Palkonyai É, Szombati I, Varga J, Poór Gy, Kiss E, Temesvári I.P.(2008) Bányászok mozgásszervi szűrővizsgálata GALS –(Gait, Arms, Legs, Spine) módszerrel. [Locomotor screening of miners with GALS –(Gait, Arms, Legs, Spine) method] *Foglalkozás-egészségügy*, 12: 132-136.
11. **Vereckei E**, Palkonyai É,Varga J, Pógyor Zs, Márton M, Böjte A, Czibalmos Á,Nagy Zs, Ratkó I, Susánszky É, Kopp M, Kiss E, Temesvári IP, MTA Bányászati Ergonómiai és Bányaegészségügyi Tudományos Bizottsága, Mozgásszervi betegségek albizottsága munkacsoportja.(2009) A mozgásszervi elváltozások és pszicho-szociális állapot felmérése a magyar bányászok körében. [Assessment of locomotor abnormalities and psycho-social condition among miners] *Bányászat*, 142:21-24.
12. **Vereckei E**, Poór Gy. Kiss E.(2010) Genetikai és immunológiai tényezők a glutenszenzitív enteropathia és az asszociált csontmetabolikus eltérések patogenezisében.

[Genetic and immunologic factors in the pathogenesis of gluten-sensitive enteropathy and associated osteometabolic abnormalities] Orvosi Hetilap, 151:372-377.

13. **Vereckei E**, Törő K, Susánszky É.(2011) Környezeti és pszichoszociális tényezők szerepének felmérése a magyar bányászok mozgásszervi elváltozásaiban. [Assessment of the role of environmental and psychosocial factors in the locomotor lesions of Hungarian miners] Foglalkozás-egészségügy, 15:11-18.

14. **Vereckei E**, Susánszky É, Kopp M, Ratkó I, Czibalmos Á, Nagy Zs, Palkonyai É, Temesvári IP, Kiss E, Törő K, Poór Gy.(2011) Környezeti faktorok és a pszicho-szociális állapot hatásának elemzése a krónikus derékfájással kezelt betegek körében. [Analysis of the effect of environmental factors and psycho-social state among patients treated with chronic back pain] Magyar Reumatol, 52:79-84.

15. **Vereckei E**, Susánszky É, Kopp M, Ratkó I, Czibalmos Á, Nagy Zs, Palkonyai É, Hodinka L, Temesvári I.P, Kiss E, Törő K, Poór G. Psycho-social, educational and somatic factors in chronic nonspecific low back pain. Rheumatol Int, (elfogadva 2012.02.29.)

Not first-author publications related to the thesis

1. Konrád K, Tátrai T, Hunka A, **Vereckei E**, Korondi I(1992) Controlled trial of balneotherapy in treatment of low back pain. Ann Rheum Dis, 51: 820-822. **IF 1.836**

2. Konrád K, Tátrai T, Hunka A, **Vereckei E**.(1992) Derékfájdalomban szenvedő betegek kontrollált kezelése balneoterápiával. Rehabilitáció, 2:27-28.

Publications unrelated to the thesis

1. Nagyhegyi Gy, **Vereckei E**, Bély M, Weis M. (1992) Többszörös extraarticularis manifesztációval, kardiális elváltozással járó rheumatoid arthritis. [Rheumatoid arthritis with multiple extraarticular manifestations and cardiac lesion.] Magyar Reumatol, 33: 193.

2. **Vereckei E**. (1999) A degeneratív ízületi és metabolikus csontbetegségek élettana, klinikuma és terápiája. [Physiology, clinical picture and therapy of degenerative joint and osteometabolic disorders] Kórház, 6:12-15.

3. **Vereckei E**, Simoncsics E, Temesvári IP, Palkonyai É, Jordan KM. (2010) A gyógyítás kormányzása Angliában a klinikus szemszögéből-Clinical governance. [The government of curing in England from the clinician's point of view – Clinical governance] IME, 9:34-38.

4. **Vereckei E**, Simoncsics E, Palkonyai É, Temesvári IP.(2009) A gyógyítás átvilágítása -klinikai audit. [Screening of curing - clinical auditing] IME,8:35-39.

5. Temesvári IP, Király M, Palkonyai É, **Vereckei E**. (2004) A kombinált Movalis terápia hatékonysága és tolerálhatósága a háziiorvosi gyakorlatban. [The efficacy and tolerability of combined Movalis therapy in the GP's practice] Háziiorvosi Továbbképző Szemle, 9:589-592.
 6. Temesvári I. P, Juhász P, **Vereckei E**, Palkonyai É. (2005) Nyaki fájdalom a járóbeteg ellátásban. [Cervical pain in outpatient care] Praxis, 14:25-30.
 7. **Vereckei E**, Kiss E.(2010) Citokinek és más mediátorok szerepe a fibromyalgia etiopatogenezisében. [The role of cytokines and other mediators in the etiopathogenesis of fibromyalgia] Immunológiai Szemle, 2: 15-18.
 8. Palkonyai É, **Vereckei E**, Simoncsics E, Temesvári IP.(2011)Új brit irányelvek a polymyalgia rheumatica, arteritis temporalis kezelésében. [New British guidelines in the treatment of rheumatic polymyalgia and temporal arteritis.]Immunológiai szemle,3:42-46.
 9. Törő K, Herjavec I, **Vereckei E**, Kovács M. (2012) Fatal idiopathic pulmonary haemosiderosis in association with pregnancy - Medico-legal evaluation. J Forensic Leg Med, 19:101-104.
 10. Gomez I, Nagy D, Seszták M,**Vereckei E**, Csauth K, Farkas P, Hodinka L.(2011)Szeptikus arthritisek diagnosztikai kihívásai két eset kapcsán. [Diagnostic challenge of septic arthritis with reference to two cases] Magyar Reumatol, 52:207-212.
- Abstracts related to the thesis that can be cited
- 1.Konrád K, Tátrai T, Hunka A, **Vereckei E**, Korondi I. (1991) Prospective controlled trial of balneotherapy in treatment of low back pain. EULAR kongresszus. Budapest
 - 3.Király M, Palkonyai E, **Vereckei E**, Veres R, Kaposi NP, Temesvári IP.(2003) Vertebraalis szegmentalis instabilitas: sikeres műteti megoldás. [Vertebral segmental instability: successful surgical intervention] Magyar Reumatol, 44: 147-179.
 - 4.Simoncsics E, Kiss E, **Vereckei E**, Palkonyai E, Fáy V.(2007) A deréktáji fájdalom kezelésének multidiszciplináris szemlélete. [The multi-discipline treatment of back pain] Magyar Reumatol, 48:150.
 5. **Vereckei E**, Palkonyai É, Simoncsics E, Polgár A, Szombati I, Varga J, Temesvári P. (2007) Bányászok mozgásszervi szűrővizsgálata GALS (Gait, Arms, Legs, Spine) módszerrel. [Locomotor screening of miners with GALS –(Gait, Arms, Legs, Spine) method] Magyar Reumatol, 48:142.
 6. **Vereckei E**, Kriván G, Réti M, Polgár A, Kiss E, Poór Gy.(2008) G. M., E Anti TNF alfa indukálta antiphospholipid szindróma manifesztálódása súlyos nekrotizáló vasculitis

képében. [Manifestation of anti-TNF-alpha induced antiphospholipid syndrome as severe necrotizing vasculitis] Magyar Reumatol, 49:141.

7. Polgár A, **Vereckei E**, Kiss E, Poór Gy. (2008) Az infekciók szerepe az autoimmun és immuno-inflammatorikus betegségek patogenezisében. [The role of infection in the pathogenesis of autoimmune and immuno-inflammatory diseases] Magyar Reumatol, 49:142.

8. **Vereckei E**, Bély M, Kriván G, Réti M, Poór G, Kiss E (2008). Anti-TNF alfa induced antiphospholipid syndrome manifested as necrotising vasculitis. (7th European Lupus Meeting, May 7 – 10. Amsterdam P79) Lupus, 17:480. **IF: 2,244**

9. **Vereckei E**, Mester Á, Hodinka L, Temesvári IP, Kiss E. (2008) Musculoskeletal manifestations of patients with long-standing coeliac disease on gluten-free diet (A cross-sectional and longitudinal study) EULAR Paris AB0671 Ann Rheum Dis, 67(Suppl II):627. **IF: 7,188**

10. **Vereckei E**, Susánszky É, Kopp M, Ratkó I, Czibalmos Á, Nagy Zs, Temesvári IP, Kiss E, Poór Gy. (2009) A mozgásszervi eltérések és a pszichoszociális állapot kapcsolatának vizsgálata derékfájással kezelt betegek körében [Evaluation of the relationship between locomotor lesions and psycho-social condition among patients treated for back pain] Magyar Reumatol, 50:165.

11. **Vereckei E**, Palkonyai É, Susánszky É, Kopp M, Ratkó I, Czibalmos Á, Nagy Zs, Temesvári IP, Kiss E, Poór Gy. (2010) Relations between musculoskeletal disorders and psycho-social state in patients with low back pain. EULAR 2010-SCIE-4667 Róma AB0795 Ann Rheum Dis, 69(Suppl3):708. **IF: 9,082**

12. Korda J, Apáthy Á, Penczner G, Winkler V, Héjj G, Sevcic K, Polgár A, Kiss EV, **Vereckei E**, Bálint P, Imre K, Nagy Gy, Kelemen J, Szűcs G, Nagy K, Náfrádi L, Bartha A, Tamási L, Fazekas K, Lukács K, Flórián Á, Spitzmüller N, Keszthelyi P, Abrudán K, Ormos G. (2011) TNF-alfa-gátló terápia során kialakuló autoimmun és vasculitises szövődmények reumatológiai betegeken Magyarországon. [Autoimmune and vasculitis complications during TNF-alpha-inhibitor therapy in patients with rheumatologic diseases in Hungary] Magyar Reumatol, 52:149.

Abstracts unrelated to the thesis that can be cited

1. **Vereckei E**, Grosz É, Hodinka B, Hodinka L. (1997) Clomipramin hatásának vizsgálata krónikus fájdalommal járó fibromyalgia szindrómában szenvedő betegeknél. [Evaluation

- of the effect of clomipramin in patients with fibromyalgia syndrome accompanied by chronic pain] Magyar Reumatol,38:162.
2. Hodinka B, **Vereckei E**, Grósz É, Hodinka L.(1998) Temperament, character and pain sensitivity in primary fibromyalgia. Reumatologia, (Warsaw) 36 (Suppl): 183.
 3. **Vereckei E**, Hodinka L, Kárpáti S, Somlai B.(1999) Rheumatoid arthritis és pyoderma gangrenosum társulása. [Concurrent occurrence of rheumatoid arthritis és pyoderma gangrenosum] Magyar Reumatol, 40:173.
 4. Király M, **Vereckei E**, Palkonyai E, Temesvári IP, Koó E, Mítuszova M.(2004) Arthritis psoriatica és köszvény, mint társbetegségek. [Psoriatic arthritis and gout as comorbidities] Magyar Reumatol, 45:159-184.
 5. **Vereckei E**, Király M, Palkonyai E, Temesvári IP, Poor Gy, Mester A, Zsary A, Janoskuti L, Farkas P.(2004) Multiplex vertebral compression or non typical non secretory myeloma? Diagnostic problems and conclusions related to a case. MagyarReumatol, 45: 41.
 6. Polgár A, Sipos A, Temesvári I P, Palkonyai É, **Vereckei E**, Reményi P, Masszi T.(2007) Allogén csontvelőtranszplantációt követően kialakult scleroderma-szerű állapot. [Scleroderma-like condition following allogeneic bone marrow transplantation] Magyar Reumatol, 48:163-164.
 7. Bászó A, Brózik M, **Vereckei E**, Kiss E, Poór Gy.(2008) Foszfolipid és oxidált-LDL elleni antitestek rizikó-szerepének elemzése lupusos és más autoimmun betegek cardiovascularis történéseiben. [Analysis of the risk-role of phospholipid and oxidized anti-LDL antibodies int he cardiovascular events of patients with lupus and other autoimmune diseases] Magyar Reumatol, 49:156.
 8. **Vereckei E**, Bászó A, Juhász M, Poór Gy, Kiss E.(2010) Diagnostic difficulties and therapeutic success in a case with primary central nervous system vasculitis. Magyar Reumatol,51:217.
 9. Juhász P, Dankó K, Fazekas K, Gaál R, Korda J, Laczkó H, Nusser N, Seregély K, Szász J, Tóvári E, **Vereckei E**, Nagy O, Poór Gy.(2010) The impact of the anti-cyclic-citrullinated peptide antibody status in the management of patients with early rheumatoid arthritis in Hungary: Results from an interim analysis. Magyar Reumatol, 51:178.
 10. Bászó A, Polgár A, **Vereckei E**, Molnár MJ, Poór G, Kiss E. (2010) Association of idiopathic inflammatory myositis and myasthenia gravis, Magyar Reumatol, 51:183.

- 11.Simoncsics E, Palkonyai É, Temesvári IP, **Vereckei E**, Jordan KM. (2010) Fájdalomcsillapítás mozgásszervi betegségekben; 550 beteg bevonásával végzett multinacionalis auditvizsgálat. Magyar Reumatol, 51:237.
- 12.Simoncsics E, Lampert K, Roux C, **Vereckei E**,Németh E, Jordan KM, Palkonyai E, Temesvari P.(2010) Pain management in rheumatology – A multinational audit with 400 patients EULAR 2010 Róma SAT0510Ann Rheum Dis, 69(Suppl3):653. **IF:9,082**
- 13.Gomez I, Nagy D, Csákvári D, Donáth J, Seszták M, **Vereckei E**,Csauth K, Farkas P, Hodinka L. (2011) Infektív arthritisek diagnosztikai kihívásai két eset kapcsán. [Diagnostic challenge of infectious arthritis with reference to two cases] Magyar Reumatol, 52:146.
- 14.Juhász P, Apáthy Á, Bálint P, Bazsó A, Donáth J, Gaál R, Héjj G,Hittner Gy, Király M, Kiss Cs, Kiss E, Korda J, Márkus I, Mester Á, Mikó I, Orbán I, Ormos G,Ortutay J, Penczner G, Polgár A,Schmidt Zs, Seszták M, **Vereckei E**,Winkler V, Poór Gy.(2011)Az Országos Reumatológiai és Fizioterápiás Intézetben biológiai terápiával kezelt rheumatoid arthritises betegeknél elért eredmények. [Outcomes of patients with rheumatoid arthritis treated with biologic therapy in the National Institute of Rheumatology and Physiotherapy] Magyar Reumatol, 52:148.