The role of balneotherapy in psoriasis rehabilitation

Doctoral (Ph.D.) theses

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Abbreviations

ADMA: asymmetric dimethylarginine

CRP: C-reactive protein

hsCRP: high sensitivity C-reactive protein

L-arg: L-Arginine

MDA: malondialdehyde

NO: nitric oxide

NOS: nitric oxide synthase

ORM: orosomucoid

PASI: Psoriasis Area and Severity Index

TAC: total antioxidant capacity

se-ORM: serum orosomucoid

u-ORM: urinary orosomucoid

WBC: white blood cell count

I. Introduction

Psoriasis is one of the most common chronic, lifelong dermatologic diseases. Due to physical and psychical symptoms, psoriasis has a considerable negative effect on quality of life. Furthermore, it has been shown that psoriasis is often associated with higher risk of developing obesity, insulin resistance, diabetes, depression, inflammatory bowel disease and some malignancies. Moreover, psoriasis is often associated with adverse cardiovascular outcomes. Several factors have been identified to play a role in the development of psoriasis. Genetical background and the onset of general risk factors (stress, obesity, smoking and alcohol consumption) can lead to an excessive activation of the immune system, which has been identified as a key factor in the development of psoriasis. Psoriasis is considered as a systemic disease, thus numerous markers of systemic inflammation have been investigated in psoriatic patients.

C-reactive protein (CRP) is a widely used marker of inflammation. Previous studies have found increased CRP levels in patients suffering from psoriasis; some of these studies suggested that CRP could be a marker of psoriasis severity. Increased CRP levels in psoriatic patients were confirmed by a meta-analysis published by Dowlatshahi et al Nevertheless, the meta-regression did not show significant association between CRP levels and psoriasis severity.

Asymmetric dimethylarginine (ADMA) is another well recognized marker of inflammation and oxidative stress. The major biological function of ADMA is the inhibition of nitric oxide synthase (NOS), which is responsible for generating nitric oxide (NO) from L-Arginine (L-Arg). L-arg/ADMA ratio is an indirect indicator of NO bioavailability. Bilgiç et al showed elevated ADMA concentrations and reduced L-arg/ADMA ratio in psoriatic patients compared to controls.

Malondialdehyde (MDA) ¬as a product of lipid peroxidation¬ is another widely used marker of oxidative stress. Relhan et al found elevated MDA levels in psoriatic patients compared to healthy controls. This was later confirmed by a larger study published by Kadam et al.

As a naturally occurring scavenger of free radicals, uric acid seems to play an important role in the antioxidant mechanisms of the body. However, according to a meta-analysis Western European psoriatic patients have significantly higher uric acid levels compared to controls.
A non-enzymatic scavenger system is a part of the defense system responsible for attenuating oxidative stress. The “activity” of this system is measured by the total antioxidant capacity (TAC). Several studies described that TAC is reduced in psoriatic patients compared to controls.

Orosomucoid (ORM) or α-1-acid glycoprotein is another major acute phase protein mainly produced by the liver, accounting for approximately 0.5-1.2g/L of serum proteins. Serum ORM

(se-ORM) levels may increase in several acute and chronic disorders in response to systemic inflammation. Elevated se-ORM has been found in patients suffering from infections, malignancies and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis and after cardiac surgery too. It appears that se-ORM is a non-specific and non-sensitive marker of inflammation. Recent studies have demonstrated that urinary orosomucoid (u-ORM) could be a more sensitive, non-invasive biomarker of inflammatory activation than se-ORM. The clinical utility of u-ORM is yet to be explored. In healthy individuals urinary excretion of ORM is low; u-ORM concentrations are 0.1-3.0 mg/L (0.01-0.3 mg/mmol if referred to urinary creatinine). Nevertheless, increased u-ORM levels have been described in certain acute and chronic diseases. The elevation of u-ORM seems to be associated with systemic inflammation and endothelial dysfunction, which are also considerable factors in the patomechanism of psoriasis.

II. Aims

II.1. u-ORM levels healthy individuals vs psoriatic patients

Comparing the u-ORM, s-ORM and CRP levels of psoriatic patients to the u-ORM, s-ORM and CRP levels of healthy individuals.

II.2. Oxidative stress markers and cardiovascular risk in psoriatic patients

Comparing the results of an oxidative stress panel - containing 6 biomarkers (ADMA, MDA, CRP, TAC, uric acid and ORM) – to cardiovascular risk in psoriatic patients. cardiovascular risk in psoriatic patients

II.3. Health insurance burden of psoriasis

We aimed to assess the Hungarian yearly health insurance burden caused by psoriasis based on National Health Insurance Fund data.

II.4. The effectiveness of balneotherapy-based psoriasis rehabilitation

We aimed to report a balneotherapy-based psoriasis rehabilitation protocol and assess its effectivity.

III. Materials and Methods

III.1. u-ORM levels healthy of individuals vs psoriatic patients

The present study was performed at our Dermatology Rehabilitation Unit between November 2016 and July 2017. Patients suffering from psoriasis with skin lesions were investigated. Exclusion criteria were impaired renal function (eGFR<60 ml/min/1.73m2), acute inflammations, autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease), any kind of biological antipsoriatic treatment and withdrawal of consent. Healthy volunteers without any kind of acute or chronic diseases were enrolled as controls. Psoriasis severity was measured by the Psoriasis Area and Severity Index (PASI) and patients were categorized based on PASI as mild (PASI<7) moderate (PASI 7-12) and severe (PASI>12) groups

Venous blood and midstream first morning urine samples were simultaneously obtained from every patient and control. Laboratory tests were performed at the university's clinical laboratory. Conventional inflammatory parameters (high sensitivity C-reactive protein (hsCRP), white blood cell count (WBC), se-ORM) were measured by routine procedures. U-ORM was determined by an automated turbidimetric assay using ORM immunoparticles. Since spot urine specimens were analyzed, u-ORM levels were divided by urinary creatinine (u-ORM/u- CREAT, mg/mmol) to avoid the influence of the variations of urinary solute concentrations caused by different hydration states.

Statistical analysis was performed with IBM SPSS Statistics for Windows Version 22. Values were compared by Mann-Whitney U test. To reveal correlations, the Spearman's test was used. All p-values less than 0.05 were considered statistically significant.

III.2. Oxidative stress markers and cardiovascular risk in psoriatic patients

The present study was performed at our Dermatology Rehabilitation Unit between November 2016 and August 2017. Inclusion criterion was the onset of psoriasis with skin lesions. Exclusion criteria were: impaired renal function (eGFR<60 ml/min/1.73 m2), acute inflammations (urinary, respiratory, skin inflammation, etc), autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease); any kind of biological

antipsoriatic treatment and withdrawal of consent. Venous blood and midstream first morning urine samples were simultaneously obtained from every patient.

Laboratory tests were performed at the university's clinical laboratory. Conventional inflammatory parameters (high sensitivity C-reactive protein (hsCRP), white blood cell count (WBC), uric acid) and serum orosomucoid (se-ORM) were measured by routine procedures. MDA levels were measured by using enzyme-linked immunosorbent assay. L-arginine, ADMA and SDMA levels were determined by liquid chromatography-tandem mass spectrometry method described by Martens-Lobenhoffer et al. U-ORM was determined by an automated turbidimetric assay using ORM immunparticles. To avoid the influence of the variations of urinary solute concentrations, u-ORM levels were divided by u-creatinine (u-ORM/u-CREAT, mg/mmol). TAC was determined by using a chemiluminescence-based method.

QRISK®2-2017 was calculated using a commercially available calculator (https://qrisk.org/). QRISK®2 score is calculated from the following parameters: age, sex, ethnicity, smoking status, diabetes status, angina or heart attack in a 1st degree relative under 60, chronic kidney disease, atrial fibrillation, on blood pressure treatment, rheumatoid arthritis, cholesterol/HDL ratio, Systolic blood pressure (mmHg), body mass index.

Statistical analysis was performed with IBM SPSS Statistics for Windows Version 22. Values were compared by Mann-Whitney U test. To reveal correlations, the Spearman's test was used. All p-values less than 0.05 were considered statistically significant.

III.3. Health insurance burden of psoriasis

The burden of psoriasis is heavy both for the individual as well as the society. It has a negative effect on the quality of life and leads to psychosocial disorders. The cost of care of the disease is high both for the patient as well as the healthcare system. The aim of this analysis is to identify the annual health insurance burden of psoriasis.

The data used for the analysis is from the National Health Insurance Fund of Hungary and is from year 2018. The data from NHIF was requested in connection with the project named 'The formation and internationalization of a network of clinical studies', request number 1043/49-2/2019.

We determined the annual insurance costs, patient traffic, the distribution of the costs by age and gender. We also analyzed number of patient number of cases, and the usage prevalence by age and gender on a yearly basis.

The following healthcare providers were analyzed: GPs, home nursing, inpatient and outpatient treatments, laboratory diagnostics, diagnostic imaging, medicine and medical device. The ICD code L4000-L4090 is used to specify psoriasis.

III.4. The effectiveness of balneotherapy-based psoriasis rehabilitation

The present study was performed at our ISO 9001 accredited Dermatology Rehabilitation Inpatient Unit from September 2016 to May 2016. Psoriatic patients who underwent a 3-week-long inward rehabilitation were enrolled. Informed written consent was obtained from every patient. The study protocol was approved by the Regional Ethics Committee of University of Pécs, Pécs, Hungary (Permission No.: 5919/2.), in accordance with the 2008 Helsinki declaration. Inclusion criterion was onset of psoriasis with skin lesions. Exclusion criteria were: having received any kind of balneotherapy within 1 year before admission, discontinuance of rehabilitation and withdrawal of consent. The severity and extent of psoriasis were measured by the Psoriasis Area and Severity Index (PASI). PASI score was calculated on admission and before discharge, after completing the 3-week-long rehabilitation. To rule out interobserver error, PASI score was assessed by the same dermatologist. Besides PASI score, high sensitive C-reactive protein (CRP) was measured from venous blood samples taken on admission and before discharge. CRP levels were determined in our university clinical laboratory with automated analyzers according to manufacturer's protocol (Cobas 8000; Roche Diagnostics GmbH, Mannheim, Germany). Besides these objective markers of disease severity, authors aimed to find out how psoriasis affects the patient's everyday life. The involved patients were asked to fill in a 0-10 scale questionnaire, which was aimed at ascertaining the patient's physical and psychical complaints (psoriasis severity, anxiety, severity of joint complaints, limitations of daily living). The questionnaire was handed out by the dermatologist on admission and before discharge. Special attention was paid to instruct the participants that the questions need to be answered regarding their current condition. Furthermore, patients were asked to read the questions carefully, to fill in all questions and to mark only one answer to every question. To rule out

potential questionnaire scaling bias, a 0-10 scale was used. Detailed medical history and list of medications were taken from every enrolled patient. During the 3-week-long inward rehabilitation, patients received a combination of spa treatments. The combination of treatments was designed individually to ease the symptoms of psoriasis and its complications; furthermore, comorbidities were treated as well. Medicinal water treatment (sulphuric water) was performed in a bath tab, for 30 min, 5 days a week. Considering the comorbidities, patients received various types of physiotherapies, electrotherapies (e.g. iontophoresis, transcutaneous electrical nerve stimulation, interference therapy), ultrasound therapies 3 times a week. UVB phototherapy, magnet therapy and transcutaneous carbon dioxide therapy were given 3 times a week in 20-min-long and 30-min long sessions. Dithranol was used 5 times a week in an ascending concentration from 0.5% to 6% according to the current dermatological status of the patient. Furthermore, sulphur (4%), carbamide (10%) and capsaicin containing (nonivamide - 0.01%) ointments were used according to current guidelines of topical psoriasis treatment. Statistical analysis was performed with IBM SPSS Statistics for Windows Version 22 (IBM Corp., New York, NY, USA). All p-values less than 0.05 were considered statistically significant.

IV. Results

IV.1. u-ORM levels healthy of individuals vs psoriatic patients

87 psoriatic patients and 41 healthy individuals were enrolled in the present study. The mean PASI of the patients was 6.52 ± 7.11. Based on PASI, 64.4% of the patients had mild psoriasis, 20.7% had moderate and 14.9% had severe psoriasis. 33.3% of the patients had positive family history of psoriasis. The mean onset of psoriasis was 26.7 ± 17.1 years. 49 patients (56.3%) had psoriasis for more than 30 years. Psoriatic arthritis occurred in 8 % of the patients (n=7). Significantly higher hsCRP levels were found among psoriatic patients when comparing the hsCRP levels of the patients to that of the controls ($p<0.001$). Significantly higher u-ORM and u-ORM/u- CREAT levels were found in patients compared to controls ($p=0.001$). On the other hand, se-ORM and WBC did not show significant differences.

Regarding psoriasis severity, significantly higher hsCRP, se-ORM and u-ORM/u-CREAT levels were found in patients with severe psoriasis compared to patients with mild and moderate symptoms. However, none of the investigated parameters showed significant differences between mild and moderate psoriasis.

Regarding complications, higher u-ORM/u- CREAT ratio was found in patients with psoriatic arthritis compared to patients without joint involvement (0.30 (0.04-0.35) mg/mmol vs 0.10 (0.06-0.20) mg/mmol), however, the differences did not meet the statistical significance (p=0.23). Neither hsCRP nor se-ORM was elevated in psoriatic arthritis patients.

IV.2. Oxidative stress markers and cardiovascular risk in psoriatic patients

114 psoriatic patients were enrolled in the present study (age 63 ± 9.98). The mean PASI of the patients was 6.52 ± 7.11. Based on PASI, 78 of the patients had mild psoriasis, 20 had moderate and 16 had severe psoriasis. 33% of the patients had positive family history of psoriasis. The mean onset of psoriasis was 25.5 ± 16.7 years. Significantly higher hsCRP and s-ORM levels were found when comparing the hsCRP and the s-ORM levels of the mild psoriatic patients to the hsCRP and s-ORM levels of the severe psoriatic patients (hsCRP, p=0.003; s-ORM, p=0.005). Significantly higher u-ORM levels and u-ORM/u-CREAT ratio were found in patients suffering from moderate psoriasis when comparing the u-ORM levels and u-ORM/u-CREAT ratio of the mild psoriatic patients to the u-ORM levels and u-ORM/u-CREAT ratio of the moderate psoriatic patients (u-ORM, p=0.003; u-ORM/u-CREAT, p=0.005). Furthermore, u-ORM levels and u-ORM/u-CREAT ratio were found to be significantly higher in patients suffering from type I diabetes compared to patients not suffering from type I diabetes (u-ORM, p=0.041; u-ORM/u-CREAT, p=0.036).

Regarding complications, significantly higher ADMA and MDA levels were found in patients suffering from psoriatic arthritis when comparing the ADMA and the MDA levels of the patients suffering from arthritis to the patients not suffering from arthritis (ADMA, p=0.021; MDA, p=0.021). U-ORM and u-ORM/u-CREAT showed significant correlation with QRISK score (u-ORM, r=0.245; u-ORM/u-CREAT, r=0.309).

IV.3. Health insurance burden of psoriasis

The highest patient number was found in connection with drug price support: 41.494 male, 43,211 female, altogether 84.705 people. This was followed by the number of patients receiving care at GPs (28.886 male, 29.307 female, altogether 58.193 people) and at outpatient treatments

(19.435 male and 20.346 female, together 39.781 people). Hospitalisation due to psoriasis was pretty low, 716 patients were admitted to acute inpatient treatment, and 183 patients to chronic inpatient treatment.

In all treatment variants case number is substantially higher, than patient number, which is due to the fact, that the same patient used the same treatment form annually more than once.

We used routinely collected data in a national database to get the figures about the incidence of different diseases in the population. The National Health Insurance Fund of Hungary has a funding database of such kind. With the help of this one we analyzed the frequency of the recourse in connection with psoriasis.

Base on the database of the NHIF the prevalence of psoriasis is 888,2 cases per 100.000 people among men and 846,2 cases per 100.000 among women, altogether 866,2. The gender ration in drug supply is 49,0% male and 51,0 female, in the demand of GP care is 49,6% male and 50,4% female. We can conclude that the prevalence of psoriasis is nearly the same among man and women.

The National Health Insurance Fund spent 2,06 billion Hungarian forints to treat psoriasis , which is equal to 7,61 million USD or 6,45 EUR. 56,5% of the costs were dedicated to men and 43,5% for women.

The main cost-components were drug-supply (64,0% among men and 54,7% among women) , outpatient treatment (19,1% among men and 24,1% among women) and GP services (6,2% among men and 7,3% among women), while all other forms of healthcare added up to 10,7% among men and 13,8% among women.

The average annual health insurance cost per patient was 27.996 HUF (103 USD / 88 EUR) for men and 20.717 HUF (77USD / 65 EUR) for women. We found bigger differences in the cost of health insurance between the two genders in the age group of 25-54.

IV.4. The effectiveness of balneotherapy-based psoriasis rehabilitation

We enrolled 80 psoriatic patients, 35 men and 45 women. All patients were diagnosed with psoriasis vulgaris and completed a 3-week-long inward dermatological rehabilitation. A total of 45 patients were suffering from early onset psoriasis and 35 from late onset psoriasis. Positive family history was found in 34% of the patients. Regarding the complications of psoriasis, atrophia psoriatica was present in 28%, while 10% of the patients were suffering from arthritis psoriatica. Thirteen of 80 patients (16%) were medicated with methotrexate and 5 of 80 (6%) received biological therapy. During the 3-week-long inward rehabilitation patients received a combination of spa treatments. Every involved patient was treated with medicinal water. The PASI score - calculated on admission and before discharge – decreased significantly after the 3-week-long rehabilitation 7.15 vs. 2.62 ($p<0.001$). The CRP level - measured on admission and before discharge – decreased significantly after the 3-week-long rehabilitation 4.1 vs. 3.5 ($p=0.026$). All considerations evaluated by the questionnaire showed significant improvement ($p<0.001$). Positive correlation was found between PASI score calculated on admission and disease severity ($r=0.439$), disease severity and anxiety ($r=0.559$) and disease severity and severity of joint complaints ($r=0.559$). Significantly lower PASI delta scores were found in patients receiving dithranol compared to patients not receiving dithranol treatment ($p<0.001$). Patients received spa treatment in a combination of at least 3; up to 8 therapies. Negative correlation was found between PASI delta and the number of spa therapies received ($r=–0.228$).

V. Discussion

V.1. u-ORM levels of healthy individuals vs psoriatic patients

Monitoring of disease activity is essential for optimal treatment and for early recognition of complications, however controlling the skin symptoms is not sufficient since psoriasis is a systemic inflammatory condition. Laboratory tests, especially inflammatory markers may be helpful in clinical decision making. Our study demonstrated that besides hsCRP, u-ORM could also be a useful, non- invasive marker in psoriasis.

To the best of our knowledge, this is the first study investigating u-ORM excretion in psoriasis. We found significantly higher u-ORM/u-CREAT levels in psoriatic patients compared to healthy individuals; moreover it might be an early and sensitive marker of psoriasis

complications, since severe cases showed higher values, and u-ORM/u-CREAT was the only marker which was able to indicate joint inflammation; however this difference did not meet statistical significance.

To date several studies investigated the connection between psoriasis severity and CRP levels. According to the meta-analysis published by Dowlatshahi et al. CRP levels are significantly higher in patients suffering from psoriasis compared to healthy individuals. However, most of the studies investigated patients with moderate or severe skin lesions (PASI>12). In our study, 64.4% of the patients had mild psoriasis (mean±SD PASI 6.52 ± 7.11); still, significantly higher hsCRP and u-ORM/u-CREAT levels were found in psoriatic patients compared to healthy controls. This can be explained by the high sensitivity of these markers, while the less-sensitive se-ORM did not show any significant elevation in psoriasis. Nevertheless, Biljan et al. found significantly higher blood ORM levels in patients suffering from psoriasis when compared plasma ORM levels of 70 psoriatic patients to 40 healthy controls. In the mentioned study, most of the involved patients had severe skin symptoms; extreme skin involvement was observed in 48.6% of the patients. In contrast, in our study the majority of the patients had mild psoriatic skin lesions se-ORM elevation. Seemingly, u-ORM is a more sensitive marker of inflammation than se-ORM, as it is capable of representing a low grade systemic inflammation in psoriatic patients. The PASI is the most widely used tool for assessing psoriasis severity, however it describes only the skin symptoms of this systemic disease. Some laboratory tests are capable of indicating systemic inflammation thus supporting clinical decision making. In this study hsCRP correlated with PASI. Moreover significantly higher inflammatory parameters were found in severe cases (PASI>12), indicating the systemic manifestation of psoriasis.

Moderate elevation of u-ORM levels were found in diabetes mellitus and also in cardiovascular diseases, presumably associated with chronic low grade inflammation, endothelial dysfunction and oxidative stress which are also pathophysiologic factors in psoriasis. It is well known that psoriatic patients have an increased risk of obesity, diabetes, cardiovascular diseases malignancies and other autoimmune diseases, these co-morbidities could influence u-ORM excretion. However, we did not find any differences regarding onset of diabetes, hypertension or other disorders and medications. Furthermore, the pathomechanism of elevated u-ORM excretion is not well clarified, although the correlations with inflammatory markers suggest that the systemic inflammation may be a crucial factor, as it has been supposed previously, too.

Asa highly sensitive, affordable and easily available non-invasive biomarker, u-ORM shows itself capable of becoming a novel inflammatory marker in psoriasis providing additional information on disease severity and progression.

V.2. Oxidative stress markers and cardiovascular risk in psoriatic patients

The increased prevalence of risk factors of cardiovascular diseases, such as metabolic syndrome, diabetes, obesity, hypercholesterolemia, hypertension and endothelial dysfunction, among psoriatic patients was described in several studies. This was confirmed by a meta-analysis published by Miller et al. According to Mehta et al severe psoriasis is responsible for an additional 6.2% absolute risk of a 10-year rate of major adverse cardiac events. In the current study 43% of the patients had high 10-year cardiovascular risk (QRISK score higher than 20%). Psoriasis is considered as a systemic immune-mediated inflammatory disease of the skin. Oxidative stress is a considerable factor in the pathophysiology of psoriasis and cardiovascular diseases.

To the best of our knowledge, this is the first study that compares the information provided by an oxidative stress panel to a cardiovascular risk score among psoriatic patients. In this paper we report the baseline values of our oxidative stress panel. Seemingly, a 10-year follow-up needs to be performed to evaluate its usefulness and feasibility. The oxidative stress panel was compiled to represent different indicators of oxidative stress. In other words, we aimed to view the same picture from different angles. CRP as a marker of general inflammation, ADMA and MDA as indirect indicators of oxidative stress, L-Arg/ADMA as an indicator of NO bioavailability, TAC and uric acid levels as indicators of free radical scavenging capability. Furthermore, we aimed to compare the levels of s-ORM and u-ORM to these recognized markers. In line with previous findings hsCRP and s-ORM levels were found to be significantly higher in severe psoriatic patients compared to mild psoriatic patients.

When comparing mild psoriatic patients to moderate psoriatic patients, significant differences could only be found in u-ORM and u-ORM/u-CREAT ratio. On the other hand, the difference of u-ORM and u-ORM/u-CREAT ratio did not reach statistical significance when comparing mild psoriatic patients to severe psoriatic patients. This can be explained with the low number of patients of severe psoriatic patients (n=16). However, the levels of non-specific inflammatory markers (s-ORM and CRP) were significantly higher in patients suffering from severe psoriasis compared to mild psoriatic patients. This indicates that in the case of severe psoriatic patients some grade of systemic inflammation is present. In our previous study both u-

ORM and u-ORM/u-CREAT ratio were significantly higher in psoriatic patients compared to controls. Taking this into account, u-ORM and u-ORM/u-CREAT ratio could be used as an indicator of low grade inflammation in mild and moderate psoriasis; as other biomarkers investigated in this study were not able to indicate the active inflammation in the case of mild and moderate psoriatic patients. However, further research is needed to clarify the clinical usefulness of u-ORM.

Another finding of our study is that there was significant correlation with u-ORM and QRISK score. The evidence on the connection between u-ORM and cardiovascular diseases is limited. Hou et al found increased u-ORM levels in patients suffering from heart failure compared to healthy controls. Other studies found that u-ORM could be a marker of endothelial dysfunction and atherosclerosis. Furthermore the urinary excretion of ORM seems to be strongly associated with diabetes mellitus, which is a known risk factor of cardiovascular diseases. This was confirmed by our study; u-ORM levels and u-ORM/u-CREAT ratio were found to be significantly higher in patients suffering from diabetes mellitus. Taking all this together, we suggest that u-ORM can be an indicator of cardiovascular risk among psoriatic patients.

V.3. Health insurance burden of psoriasis

In our analysis we assessed the burden of psoriasis within the social health insurance based on the data from National Health Insurance Fund of Hungary.

In Hungary, Rencz and partners studied the expenses connected to psoriasis, by analyzing a smaller patient population. Their research was conducted with the data collected in two dermatological institutes via questionnaires. The 57 patients enrolled into the study (65% male) with the average age of 54,3+-11,6 years, life quality of EQ-5D, measured by life quality index 1,48+-0,4. Annual average expenses per patient was 2,56 million HUF out of those 71% was connected to biological therapy and 21% to indirect expenses. 95% of the indirect expenses, 506 thousand HUF / patient / year was connected to drop-out from work. (82) There were less patients enrolled in their study (57 people), but they conducted a more detailed analysis which incorporated life quality analysis as well.Research from Denmark also shows, that drug expenses

are the most significant from the expenses connected to psoriasis, 83,5% of it connected to biological therapy. (83) Diseases linked to psoriasis also have a heavy insurance burden. (84)
In case of balneotherapy there is an emerging significance of scientifically proven therapies. (85, 86, 87). Bender and partners proved the effectiveness of balneotherapy with a meta analysis. (88)
The uniqueness of our burden of illness study lies in the fact, that we used a national database to assess the demand and the expenses. The Hungarian Health Insurance Database offers a unique opportunity even on an international level to conduct burden of illness studies.

V.4. The effectiveness of balneotherapy-based psoriasis rehabilitation

This study demonstrated that the PASI scores and the CRP levels decreased significantly as a result of the 3-week-long rehabilitation. Baros et al. performed a study to compare the results of balneotherapy, standard treatment and combination treatment. The application of combined treatment showed the best short- and long-term results. However, this study did not involve inward rehabilitation and included a smaller, heterogenic population. To the best of our knowledge, this is the first publication which reports experiences of balneotherapy in inward psoriasis rehabilitation. The aim of the 3-week-long rehabilitation was to not only to ease the symptoms of psoriasis, but also to treat the patient's comorbidities. Taking into account that most of the patients involved were suffering from the symptoms of musculoskeletal diseases various types of physiotherapies, electrotherapies and ultrasound therapies were given to reduce the patient's musculoskeletal symptoms. Furthermore, every patient received medicinal water treatment, as it is the essential component of spa treatment. Medicinal water has been used for centuries to cure dermatological diseases particularly psoriasis. In vitro studies showed that medicinal water is capable of modulating the immune system, moreover sulfur waters can inhibit the proliferation of Tlymphocyte, the release and production of interleukin-2 and interferon gamma. Furthermore, sulfur waters can inhibit the TNF-α induced expression of E-selectin and ICAM-1, which are mediators of psoriasis related inflammation. Exogenous hydrogen sulphide has been shown to reduce clonal growth, cell proliferation and cell adhesion of human keratinocytes in psoriasis. Boros et al. have found increased somatostatin release in psoriatic patients after sulfuric medicinal water treatment, which can be another possible explanation of anti-inflammatory mechanisms of sulfuric water. Moreover, the antiinflammatory effects of

medicinal water are effective not only in psoriasis, but also in several musculoskeletal diseases (e.g. rheumatoid arthritis, fibromyalgia, ankylosing spondylitis). To enhance the beneficial effects of medicinal water on psoriasis, phototherapy (UV-B light) was used. According to previous studies, phototherapy is capable of inhibiting the proliferation of keratinocytes and suppressing the adverse T cell differentiation observed in psoriasis. In conclusion, after completing the 3-week-long spa therapy-based rehabilitation, PASI score showed improvement in psoriasis. Three-week-long rehabilitation was capable of reducing inflammation, which is indicated by the decrease in CRP levels. The complex spa therapy used during the rehabilitation is an effective tool to reduce the symptoms of psoriasis and improve the patient's well-being.

VI. Theses

- We published the first study investigating u-ORM excretion in psoriasis

- We found significantly higher u-ORM and u-ORM/u- CREAT levels in patients compared to controls

- We found significantly higher hsCRP, se-ORM and u-ORM/u-CREAT levels in patients with severe psoriasis compared to patients with mild and moderate symptoms.

- We composed an oxidative stress panel - containing 6 biomarkers – which could be capable of multi parameter monitoring of oxidative stress among psoriatic patients

- We first described the significant correlation between u-ORM and u-ORM/u-CREAT and QRISK score.

- We were the first ones to describe the correlation between u-ORM and u-ORM/u-CREAT ratio and the 10 year stroke and myocardial infarcts risk assessment QRISK2-2017 poinsystem results.

- We reported an inward balneology based psoriasis rehabilitation protocol and assessed its effectivity

VII. Publications

Publications related to the theses

1. Péter Iván, Jagicza Anna, Ajtay Zénó, Kiss István, Németh Balázs. A psoriasis és az oxidatív stressz. **Orvosi Hetilap** 157:(45) pp. 1781-1785. (2016) (Q3; IF=0,349)
2. Péter Kustán, Tamás Kőszegi, Attila Miseta, Iván Péter, Zénó Ajtay, István Kiss, Balázs Németh. Urinary Orosomucoid A Potential Marker Of Inflammation In Psoriasis. **International Journal of Medical Science** 15:(11) pp. 1113-1117. (2018) (Q1 IF= 2,284)
3. Iván Péter, Anna Jagicza, Zénó Ajtay, Imre Boncz, István Kiss, Katalin Szendi, Péter Kustán, Balázs Németh. Balneotherapy in Psoriasis Rehabilitation. **In Vivo** 31(6):1163-1168 (2017) (Q2 IF=1,116)
4. Urinary Orosomucoid: A New Marker Of Cardiovascular Risk In Psoriatic Patients? közlésre benyújtva -**Therapeutics and Clinical Risk Management**

Impact factors of publications related to the theses:(2018): 3.749

Balázs Németh, István Kiss, Tímea Jencsik, Iván Péter, Zita Kreska, Tamás Kőszegi, Attila Miseta, Péter Kustán, Zénó Ajtay. Angiotensin converting enzyme inhibition improves the effectiveness of transcutaneous carbon dioxide treatment. **In vivo** 31:(3) pp. 425-428 (2017) (Q2 IF=1,116)

Balázs Németh, Lóránd Kellényi, István Péterfi, Tamás Simor, Diána Ruzsa, Holczer Lőrinc, István Kiss, Iván Péter, Zénó Ajtay. New Validated Signal-averaging-based Electrocardiography Method to Determine His-ventricle Interval. **In vivo** 30: 899-903 (2016) (Q2; IF=0,953)

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