## Research Paper

### Sulphurous Mud-Balneotherapy: an Possible Strategy for the Plaque Psoriasis

<table>
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<tr>
<th>Name</th>
<th>Institution</th>
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#### KEYWORDS

Plaque Psoriasis, Mud-balneotherapy, Oxidative Stress.

### ABSTRACT

The aim of this observational pilot study was to evaluate effectiveness, safety and a possible antioxidant effect of sulphurous mud-balneotherapy in patients suffering from plaque psoriasis. The study was conducted on a sample of 58 subjects (50% women and 50% men) with a mean age of 52±13 years (age range 14-78 years) divided into 2 groups: A and B. The psoriatic patients of group A (n=33) was subjected to sulphurous mud-balneotherapy. In the patients of group B(n=25), composed of subjects with plaque psoriasis in pharmacological topical therapy, was associated the mud-balneotherapy carried out in the same way and modality in which it was made in the group A. After 2 weeks were assessed: the PASI index (Psoriasis Area and Severity Index), the impact of the treatments used on quality of life for psoriatic people tested by the DLQI questionnaire and plasma concentration of ROMs (by d-ROMs Test, Diacron-Grosseto-Italy). The data collected at the end of mud-balneotherapy (group A) as compared to basal values have shown a significant (p<0.05) reduction of PASI score, DLQI score and plasma [ROMs]. The association pharmacological topical therapy and sulphurous mud-balneotherapy (group B) induced a significant (p<0.05) decrease of DLQI score and plasma [ROMs] in greater percentage as compared to group A, whereas for PASI score in groups A and B was demonstrated significant equal reduction. In conclusion, the results of this study show that the sulphurous mud-balneotherapy can play an important role in the therapeutic strategy of plaque psoriasis to the benefit of an improved quality of life.

### 1. Introduction

Plaque Psoriasis is a chronic, inflammatory skin disease, non-contagious, and recurrent [1]. In the general Italian population it is estimated a prevalence of 2.8%, with a significant socio-economic impact according to a study of drug-economics, which considered the direct and indirect costs of the disease [2-5]. The Italian National Health Service spends on average about € 8371.61 for the most severe cases of psoriasis to the benefit of an improved quality of life. Psoriasis has a multifactorial pathogenesis, in which predisposing genetic factors (the dysregulation of the immune system and the alteration of keratinocytes), and environmental trigger factors (such as local trauma, typically streptococcal infections, emotional stress, drugs β-blockers, lithium, antimalarials, NSAIDs, progesterone, estrogen at high doses, smoke, etc.) interact with each other by triggering a specific immune response mediated by T lymphocytes [10-13]. Various studies have also shown the importance of oxidative stress in the induction of psoriasis by increased production of free radicals and / or decreased function of the endogenous antioxidant defenses of the organism [14-17]. In people with psoriasis has been described the establishment of an oxidative environment both at a systemic level and at the local level of plaques, a condition due to a massive release of reactive oxygen species (ROS) by neutrophils [14]. Still in psoriasis, as well as in other inflammatory diseases of the skin, antioxidant defenses are greatly reduced. In fact, we find lower levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), ascorbic acid in people with psoriatic skin compared to that of normal subjects [17]. A recent study [18] in patients with psoriasis has shown, increased protein glycation and stimulation of the immune system in response to glycation end-products. The research found, in patients with psoriasis in the ac-
tive phase of the disease, a significantly higher concentration of AGE-peptides (substances resulting from the processes of glycation with malicious action on cell permeability) and antioxidative enzymes were observed. The compound is not toxic to topical therapy alone, systemic pharmacological therapeutic aids reserved for the most severe and extended forms of psoriasis including the use of oral or parental administration of immunosuppressive drugs such as methotrexate or cyclosporine, retinoids, etc., and in cases of contraindication or ineffectiveness of the latter can be used in these severe forms biologic drugs such as adalimumab, etanercept, infliximab, etc. Recent research has shown that interventions through therapeutic hypnosis (the Ultradian Healing Response) and meditation (the Relaxation Response) reduces stress and promotes healing on the molecular-genomic level [24-30]. From the literature the importance of the “creno-therapy” (from the greek crené-source) or “spa Medicine” is deduced in numerous dermatologic affections. Spa Medicine uses natural mineral waters, with different modes of use and applications [6,31,32]. In the field of dermatology spa Medicine comprising the use of mineral water in the form of balneotherapy and/or mud-bath therapy seems to give, in mild to moderate cases of psoriasis, satisfactory results [6,33-40] with improvement of the clinical and psychological symptoms of the patients’, and good compliance and tolerability with rare adverse effects, which is useful in the treatment of chronic diseases such as psoriasis. Literature data [41-47] show a possible antioxidant effect of mineral waters, in particular those sulphurous [41,42,44-47]. A personal research [41] has highlighted, in healthy rats, the ability of the drinking therapy with sulphurous mineral water to significantly reduce the plasma concentration of reactive oxygen metabolites (ROMs) versus tap water; moreover other studies [42,43] have shown a protective effect induced by sulphurous mineral water against oxidative DNA damage in inflammatory respiratory diseases due to the reducing properties of the sulfhydryl groups in it. In retrospective studies [44,45] the sulphurous mineral waters have demonstrated antioxidant effect and positive action on the oxidative defense mechanism in rabbits and rats. Therefore, considering that studies regarding the effectiveness and safety of mineral water used in the form of mud-balneotherapy in plaque psoriasis are still insufficient [37,39], considering the data of the literature that highlight the important role of oxidative stress in psoriasis and considering the possible anti-oxidant action of sulphurous mineral waters as demonstrated by various researches, the purpose of this pilot observational study was to verify the effectiveness of mud-balneotherapy with sulphurous water, alone or in association with pharmacological topical treatment, in subjects suffering from plaque psoriasis, the most common clinical form of psoriasis.

2. Materials and Methods

In our pilot observational study was considered a sample of 58 patients suffering from plaque psoriasis. Informed consent was obtained from all subjects and the research project was based on the guidelines of the Declaration of Helsinki. The subjects of the test sample, included 29 (50%) female and 29 (50%) male, with a mean age of 52±13 (age range: 14-78 years), who presented themselves to our observation with a diagnosis made by a specialist. The enrolled psoriatic subjects were divided into 2 groups respectively called A and B whose characteristics are reported in Table 1.

The patients in group A (n=33) were subjected, in the morning preferably on an empty stomach, to a cycle mud-balneotherapy using sulphurous mineral waters in Italian spas (Telese spa in Telese Terme-Benevento and Rosapepe spa in Contursi Terme-Salerno). The application of mud on the body was done to the skin of the area(s) to be treated at a temperature of 35°C. The duration of each application was 10-12 minutes. At the end of the session, patients received, after a cleansing shower with normal water, a bath at a temperature between 36-37°C for a duration of 15 minutes. Subsequently, the patient has gone in individual cabin where, suitably covered, has rested for 20-30 minutes lying down or reclined. This stage of treatment is called “reaction”. The subjects in group B (n=25) carried out a pharmacological topical treatment with drugs usually used in psoriatic disease (clobetasol, flumethasone, momethasone, betamethasone, calcipotriol, calcitriol, taccitol, hydrating cream) prescribed by their general practitioner or by specialist in dermatology. In addition the pharmacological treatment was associated with a cycle sulphurous mud-balneotherapy carried out as in group A.

After two weeks of treatment in each patient of the two groups identified (A and B) were detected the following parameters:

a) ADVERSE EVENTS

b) PASI index (Psoriasis Area and Severity Index) [48], used clinically to assess the severity of psoriatic disease.

c) Impact of the therapeutic cycle considered on the QUALITY OF LIFE of the subjects examined by the administration of the questionnaire “Dermatology Life Quality Index” (DLQI), used by Finlay also at the spa [49,50]. The DLQI is a specific question-naire comprising 10 questions through which it is possible to analyze the problems related to therapies for psoriasis, psoriasis interference with daily activities and relationships. The DLQI ranges from a minimum score of 0 (no interference of the disease) to a maximum score of 30 (maximum involvement of the disease on quality of life). The higher the score worse the quality of life of the subject.

d) PLASMA CONCENTRATION OF REACTIVE OXYGEN METABOLITES (ROMs): measured by the d-ROMs test (Diacon, Grosseto, Italy) performed with dedicated analytical system (FREE System- Florence Spectrophotometer Slim SEAC) on peripheral capillary blood. The d-ROMs is a spectrophotometric test used to determine the concentration of ROMs, primarily hydroperoxides (ROOH) generated in cells from the attack of oxidative reactive oxygen species (ROS) on various biochemical substrates (carbohydrates, lipids, amino acids, proteins, nucleotides, etc.) [51,52]. The ROMs are relatively more stable than reactive oxygen species (ROS) and therefore more easily detected and quantified by analytical procedures [51]; moreover ROMs can be considered markers of early oxidative damage for the generation of two highly reactive oxidants radicals, the alkoxyl and alkylperoxy, which in turn promote the oxidative cascade [51,53]. The detailed description of the technique of relief is in Costantini and Dell’Omo [54,55]. The results of d-ROMs test were expressed in arbitrary units called “Carratelli constant” (CARR.U.), where 1 CARR.U corresponds to 0.08 mg of H2O2 / 100mL (48,49). It should be noted that in healthy subjects the plasma concentration of ROMs comprises a range of 250-300 CARR.U. [51,52].

3. Statistical Analysis

The general characteristics of the population included in the study were analyzed using descriptive techniques. In all the variables evaluated the data obtained were expressed as the arithmetic mean ± standard deviation (SD). The results were compared with Student’s “t” test, normally distributed data and with the Wilcoxon-Mann-Whitney test in data with non-normal distribution. P values ≤ 0.05 were considered statistically significant [56].

3. Results

3.1 Adverse events

The collected data showed in psoriatic patients treated in sulphurous mud-balneotherapy, alone (group A) or in combination with drug therapy (group B), good local and systemic tolerability with absence of mortality; not increase of itch; absence of nausea, malaise, vomiting, dizziness, diarrhea, headache,
ache, dry mouth. In one subject in group A was observed dizziness mild and of short duration in second day of treatment.

3.2 PASI index
At the end treatment, in groups A and B, a significant (p<0.05) reduction PASI score (group A: 10±9→5±5 - group B: 8±8→4±4) (Table 2) is observed in comparison to the basal values. The comparison between the mean values of PASI score in group B versus group A detected after treatment showed decrease found not significant (p<0.05) (Figure 1).

3.3 Impact on quality of life
In Figure 2 are reported the mean values±SD of the maximum score of the questionnaire DLQI detected in the two groups of subjects with psoriasis considered before and after treatment. The analysis of the data showed a significant (p<0.05) reduction of the total score DLQI in the treated groups (group A: 5.4±4.3→3.3±3.1 and group B: 6.8±3.9→3.5±2.5) at the end treatment versus basal values (Figure 2). The comparison between the mean values of the DLQI score in group B versus group A measured after treatment demonstrated not significant variation (p<0.05) (Figure 3).

3.4 Effects on plasma concentration of reactive oxygen metabolites ([ROMs])
At the end treatment in groups A (sulphurous mud-balneotherapy only: 404 CARR.U.±47→363±54) and B (association sulphurous mud-balneotherapy + pharmacological topical therapy: 351 CARR.U.±47→300.CARR.U.±46) a significant (p<0.05) reduction of plasma [ROMs] is observed in comparison to the basal values (Table 3). The comparison between the mean values of the [ROMs] measured after treatment in group B versus group A demonstrated significant (p<0.05) reduction (Figure 4).

4. Discussion
Plaque psoriasis, the most common clinical form of psoriasis, is an inflammatory, chronic, immune-mediated disease. It affects about 90% of patients with psoriasis and 20-30% of cases are of a moderate-to-severe degree. In light of current scientific knowledge it is clear that genetic predisposing factors and environmental triggers interacting with each other would be able to induce an enormous acceleration of the replacement of epidermal cells in addition to vascular inflammation and hyperplasia. It was also shown a close correlation between oxidative stress and inflammation in psoriasis [14,15]. Further studies are required to know whether proper management of oxidative stress at mild stage can help to reduce the progression of the disease [57]. At present for this chronic condition, there is no definitive cure. However, there are several methods, classic and innovative to try to control it. The therapeutic drug modalities as well as treatments with ultraviolet methods, classic and innovative to try to control it. The therapeutic effects which can be summarized as: exfoliating and keratolytic action on the stratum corneum resulting in peeling effect (sulphhydryl ion is able to reduce, and therefore to split, the disulphide bonds of cystine, which take aggregated molecules of keratin, freeing the two molecules of cysteine) [6,31,40,61]; anti-inflammatory and immunomodulatory action (by stimulation of the reticuloendothelial system; by reduction of release of pro-inflammatory cytokines, that significantly contribute to pathological psoriatic damage as interferlein 8, by hydrogen sulfide; in vitro studies have shown a dose-dependent inhibitory effect of mineral waters such as “sulphurous” on blastization and proliferation of T lymphocytes obtained from the peripheral blood of both normal subjects and patients with chronic inflammatory syndromes of the upper respiratory tract as well as articular and peri-articular); stimulation of cutaneous tropism [40,62-65].

The bicarbonate ions are able to normalize the cutaneous pH generally impaired in the presence of exudative-degenerative processes which helps to reduce the itching and skin irritation; Add to that the moisturizing cutaneous action of magnesium as well as its ability to help the maturation and differentiation of keratinocytes and the disinfectant action of chlorides [66-68].

The pressure and temperature of the bath stimulate the blood vessels bringing a general feeling of improved well-being to the whole body [61,69]. Moreover, in agreement with literature data [57], which reveals that the proper management of oxidative stress in psoriasis may help decrease the progression of the disease, our research has shown that the use of sulphurous mud-balneotherapy may be an effective strategy in this disease for the antioxidant effect observed.

5. Conclusion
In conclusion the results of our study show that in a chronic disease such as plaque psoriasis of mild to moderate degree, the sulphurous mud-balneotherapy (which uses natural substances with limited unwanted adverse events; good local and...
systemic tolerability; positive compliance; a possible antioxidant effect; reduction of PASI index and DLQI score) may be a viable alternative or a adjunctive therapy to pharmacological topical treatments, steroids in the first place, both to give a break to drug and/or reduce the drug dosage. In fact in long term treatment it is necessary to balance the benefits with the risks of potential adverse events of protracted drug therapy. Therefore the use of sulphurous mud-balneotherapy should be taken into due account in the treatment strategies for diseases that require prolonged use of drugs, so that doses and frequency of administration can be reduced. Recently the WHO (World Health Organization) has included spa therapy among the strategies and goals of traditional medicine [70].

Conflict of Interests
The authors declare that there is no conflict on interests regarding the publication of this paper.

Figure 1 – Comparison between the mean values ±SD of PASI score detected after treatment in group B (drugs+mud-balneotherapy) versus group A (mud-balneotherapy).

Student’s t test unpaired *p<0.05 - **p<0.01

Figure 2 – Comparison of mean values ±SD of maximum score of DLQI questionnaire detected at the end treatment vs baseline in two groups (A and B) of psoriatic subjects considered.

Wilcoxon Signed-Ranks test for paired samples *p<0.05 - **p<0.01

Table 1 - Generality of the two groups of psoriatic patients (A and B) considered: descriptive statistics.

<table>
<thead>
<tr>
<th>NUMBER OF CASES</th>
<th>GROUP A</th>
<th>GROUP B</th>
</tr>
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<tbody>
<tr>
<td>N=33</td>
<td></td>
<td>N=25</td>
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<tr>
<td>AGE (years)</td>
<td></td>
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<tr>
<td>Mean ±DS</td>
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<td>Median</td>
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<tr>
<td>Minimum</td>
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<tr>
<td>Maximum</td>
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<table>
<thead>
<tr>
<th>SEX</th>
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<tbody>
<tr>
<td>male (%)</td>
<td>16 (48%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>females (%)</td>
<td>17 (52%)</td>
<td>12 (48%)</td>
</tr>
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</table>

Table 2 – Comparison of mean values ±SD of PASI score detected at the end treatment vs baseline in two groups (A and B) of psoriatic subjects considered.

<table>
<thead>
<tr>
<th>Group</th>
<th>PASI score before treatment (mean±SD)</th>
<th>PASI score after treatment (mean±SD)</th>
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<tbody>
<tr>
<td>A (cycle mud balneotherapy)</td>
<td>10 ± 9</td>
<td>5 ± 5 **</td>
</tr>
<tr>
<td>B (pharmacological topical treatment + cycle mud-balneotherapy)</td>
<td>8 ± 8</td>
<td>4 ± 4 **</td>
</tr>
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</table>

Student’s t test paired *p<0.05 - **p<0.01

Figure 3 – Comparison between the mean values ±SD of maximum DLQI-score detected after treatment in group B (drugs+mud-balneotherapy) versus group A (mud-balneotherapy).

Mann-Whitney test for independent samples *p<0.05 - **p<0.01

Figure 4 - Comparison between the mean values ±SD of plasmatic reactive oxygen metabolites ([ROMs]), expressed in CARR.U., detected after treatment in group B (drugs+mud-balneotherapy) versus group A (mud-balneotherapy).
Table 3 – Comparison of mean values ± SD of plasmatic reactive oxygen metabolites ([ROMs]), expressed in CARR.U., obtained before and after treatment with sulphurous mud-bath therapy alone (group A) or in association with pharmacological topical therapy (group B) in psoriatic subjects observed.

<table>
<thead>
<tr>
<th>GROUP CONSIDERED</th>
<th>[ROMs] (mean ± SD) before treatment</th>
<th>[ROMs] (mean ± SD) after treatment</th>
<th>Student’s t test paired *p&lt;0.05 - **p&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (mud-balneotherapy)</td>
<td>404 CARR.U. ±68</td>
<td>363 CARR.U. ±54*</td>
<td>p=0.016</td>
</tr>
<tr>
<td>B (pharmacological topical treatment + cycle mud balneotherapy)</td>
<td>351 CARR.U. ±47</td>
<td>300 CARR.U. ±46*</td>
<td>p=0.035</td>
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