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TRACE ELEMENTS HOMEOSTATIC IMBALANCE IN MILD AND SEVERE *PSORIASIS*: A NEW INSIGHT IN BIOMARKER DIAGNOSTIC VALUE FOR *PSORIASIS*

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Abstract
Introduction: The pathogenesis of psoriasis remains elusive and is a subject of interest to clinicians and scientists. Many studies have thrown light on the etiopathogenesis of psoriasis at both molecular and tissue concentrations. Of these, the role of trace metals has been of interest.
Objective: To evaluate the possible role of trace elements in mild and severe psoriasis.
Patients: Sixty patients suffering from psoriasis were included in the study and 30 healthy subject served as a control.
Methods: Serum sample analysis for some trace elements namely Na, K, Ca, P, Cu, Zn, and Fe using inductively coupled plasma-atomic emission spectroscopy (ICP-AES). In psoriatic patients and control, the severity of psoriasis was assessed by psoriasis area severity score (PASI score).
Results: In psoriatic patients the level of serum calcium and zinc were diminished while the level of serum copper, iron and organic phosphorous were increased. These changes were significantly evident in severe psoriasis compared to control and mild psoriasis ($P<0.05$).
Conclusions: There may be a role for trace elements in the etiopathogenesis of psoriasis.

Key words: psoriasis; trace elements; serum; homeostasis

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Introduction

Psoriasis is a hyperproliferative cutaneous disease of multifactorial etiologies: genetic background, environmental factors, vascular and immune system disturbances [1-3].
The clinical course is unpredictable, characterized by remissions relapses. Lesions are typically well-demarcated erthymatous, scaly plaques. Histopathologically,there is marked epidermal hyperplasia (acanthosis) accompanied by retention of keratinocytes nuclei in the stratum corneum (parakeratosis) and a mixed dermal infiltrate, including CD4+ T cells, dendritic cells, macrophages, and mast cells. Neutrophilic exudates are often seen (Munro microabscesses) and CD8+ T cells are present in the epidermis. Dermal papillary blood vessels are dilated and tortuous, and there is increased expression of angiogenesis-associated genes [4-7].
The pathogenesis of this disease remains elusive.
Trace elements are those found in such small amounts in the living tissues, of the trace element appearing in the body, ten have been designed essential trace elements: Zinc, copper, manganese, iodine, iron, cobalt, molybdenum, tin, selenium and chromium [7-9].
Although, by definition, trace elements are required in minutely small doses (less than 100mg/day) this does not mean they can be ignored. Trace elements are among the most important factors in maintaining and recovering health [10,11] .
In analytical chemistry, a trace element is an element in a sample that has an average concentration of less than 100 parts per million measured in atomic count, or less than 100 micrograms per gram.
In biochemistry, a trace element is a dietary mineral that is needed in very minute quantities for the proper growth, development, and physiology of the organism [12].

Aim of the work

The aim of this work is to detect any possible changes in the metabolism of some trace elements and their relation to the etiopathogenesis of psoriasis.

Patients and Methods

Sixty patients suffering from psoriasis and 30 healthy subject served as a control (age, sex, body mass index matched with the patients) were included in the study.

They were randomly selected from the outpatient clinic of dermatology and venereology department, Alexandria Main university hospital, they are subjected to:

1. History taking including: age -sex - occupation -duration of the disease -family history -history of drugs- predisposing factors like stress or trauma -receipt of previous of treatment.

2. Clinical examination including: morphology -distribution -extent of involvement -severity of the lesion.

- The selection criteria and the protocol were approved by Alexandria ethics committee.
- All the participants in the study signed an informed consent.

Inclusion criteria:

-Male and female patients aged from 13 to 65 y (mean age 33.61 ± 17.12y.o.) with a clinical diagnosis of psoriasis of different severity.
-All patients had chronic psoriasis of different location on the upper extremities, lower extremities, and /or the trunk.
-An overall treatment free period of at least 2 weeks after any topical antipsoriatic (anthralin, corticosteroids, calcipotriol, retinoids) treatment and at least 2 months after systemic therapy (cyclosporines,methotrexate, retinoids, hydroxyurea, macrolides, corticosteroid, fumaric acid, biologics) must have elapsed before start of the work.

Exclusion criteria:

-patients with any chronic systemic diseases affecting the metabolism.
-patients with history of prolonged drug intake for any disease.
-recent phototherapy or systemic antipsoriatic treatment within the last 2 months before launching the work.
-recent topical antipsoriatic treatment within the last 2 weeks before launching the experiment except for Vaseline as an emollient.
-pregnancy and women using contraceptive pills .
-patients on vitamins or mineral therapy.

Assessment of the extent and severity of psoriasis:

The psoriasis area and severity index (PASI) score was first described in 1978 as a method of quantifying the extent of psoriasis and since then has been used frequently to assess disease severity [13].

- Psoriasis was graded according to the Psoriasis Area Severity Index (PASI), presenting at the time of blood collection. Among study patients, 30 subjects (50%) were with severe psoriasis (PASI range from 13-18), and another 30 (50%) with mild psoriasis (PASI range from 3-12). Patients (n=60) were assessed in comparison with the control group (n=30). The control group presented no clinical problems.

Venous blood samples (3–5 ml) were collected using metal-free Safety Vacutainer blood collecting tubes (Becton Dickinson, Rutherford ®, USA) containing >1.5 µg K2EDTA/ml and were stored at −20°C until analysis.

Seven trace metals: sodium (Na), potassium (K), Calcium (Ca) phosphorous (P), iron (Fe), Zinc (Zn) and Cupper (Cu) were estimated by atomic absorption spectrophotometrically following method of Fuwa et al [14], and Rodushkin [15].

Statistical analysis of the data

The clinical and laboratory results obtained are statistically analyzed using SPSS/PC* (Statistical package for social science for personal computers).Student's t- test was used and data were expressed as mean ± S.D, and $P<0.05$ was considered statistically significant.

Results

The studied patients aged from 13 to 65 y with a mean age of 33.61 ± 17.12 y.o.

The study was conducted on thirty (50%) male and thirty (50%) female patients.

The PASI score: severity of psoriasis was classified as mild in 50% of cases (PASI score rage from 3 – 12 with a mean of 7 ± 1.31.

Severe psoriasis in 50% of cases (PASI score rage from 13 – 18 with a mean of 11± 2.55.

The serum level of the 7 trace elements in psoriatic and control subjects (Tabl. I).

	Mild psoriasis	Severe psoriasis	Normal control	P value
No of cases	30	30	30	
Sodium (mmol/L) (Mean ± SD)	140±1.6	142.5± 3.1	136.5±4.6	0.14
Potassium (milliEquivalents per liter (mEq/L) (Mean ± SD)	4.51±0.5	3.72± 1.4	3.56± 0.7	0.07
Calcium (mg/dl) (Mean ± SD)	7.25±0.64	6.5±0.33	9.84±0.81	0.01*
phosphorous(mg/dl) (Mean ± SD)	5±1.26	6±0.74	3.55±0.48	0.02*
Iron (µg/dl) (Mean ± SD)	178±3.21	180±4.19	170±6.1	0.011*
Zinc (µg/dl) (Mean ± SD)	79.2± 2.3	70.3±1.55	86.7±8.4	0.031*
Copper (µg/dl) (Mean ± SD)	25±2.3.4	27±1.6	20±4.1	0.021*

Table I. The serum level of the 7 trace elements in psoriatic and control subjects.

*** P < 0.05 statistically significant**

No significant differences between the serum level of sodium and potassium in patients and controls (P>0.05)
The serum calcium and zinc levels were significantly diminished in psoriatic patients especially in severe psoriasis (P < 0.05).
The serum organic phosphorous, iron and copper levels were significantly increased in psoriatic patients especially in severe psoriasis (P < 0.05).
By correlation analysis no noticed effect of age, sex and body mass index on the previous results.

Discussion

Psoriasis is a chronic skin disease of multifactorial etiology. The exact pathogenesis of psoriasis has remained unclear, but some factors are known to trigger, participate or aggravate the disease process [3-6].
The stages of psoriasis as mild, moderate and severe are based on the PASI score. The PASI is a useful tool in monitoring response to treatment [13].
Normal trace (minerals) elements in the blood are important for maintenance of skin health, abnormality of trace elements can lead to many diseases [10,16]. Minerals play important role in the subtle biochemistry of the body as do vitamins [9,16]. Virtually, all enzymatic reactions in the body require minerals as cofactors [16].
Oxidative stress can result from deficiency of trace elements such as zinc, copper and selenium [11,16].
Trace elements and their compounds have been used since ancient times for their therapeutic as well as cosmetic effects on the skin [8,9]. The unique process of keratinization and melanin formation is enzyme-dependent and therefore could be influenced by trace element deficiencies or excesses as trace elements are involved in enzymatic activities and immunologic reactions [10].
We measured some of the trace elements in order to illuminate the possible role of trace metals in the pathogenesis of psoriasis. This study was conducted on 60 patients with psoriasis of different severity. And 30 healthy volunteer. On measurement of serum trace elements it was found many abnormality. The most important notice was that diminished serum calcium level in psoriasis mainly in severe type and this in agreement with the study done by Herizchi 2007 [17] and this inforced by the effect of calcipotriol in the treatment of psoriasis [17,18].
It is a must for every psoriatic patients to measure serum calcium and treatment by calcium if possible.
Also serum organic phosphorous level was found to be increase in a large percentage of psoriatic patients mainly in severe psoriasis, this in accordance to Sreekantha [18].
Hypocalcemia is responsible for triggering and aggrevation of psoriasis [19]. Calcium within the cell plays an important role in the regulation of proliferation and differentiation of keratinocytes. Calcium homeostasis may be involved in the development or exacerbation of psoriasis because hypocalcaemia may damage cell adhesion molecules, such as cadherins which were dependent on calcium [19,20].
In this study it was found that the serum level of free reactive serum iron was elevated especially in severe psoriatic patients, the same results were found by Arpita Ghosh 2008 [21]. In psoriatic plaque blood capillaries are dilated and become tortuous to form loops which may cause break down of erythrocytes to release hemoglobin also low level of glutathione peroxidase and super oxide dismutase may help to elevate the level of hydrogen peroxide which further causes break down of heamoglobin within erythrocytes to form non heme reactive iron. This free reactive iron can catalyze Haber-Weiss reaction and generate deadly damaging hydroxyl radical which in turn damaging cellular constituents [21,22]. However Nathalie et al in their study found that Iron serum concentrations were normal in psoriatic patients and in healthy subjects, whereas iron concentrations were high in psoriatic involved and uninvolved dermis compared to healthy dermis [23].
Serum zinc level was found to be diminished in a considerable percentage of psoriatic patients mainly in severe psoriasis and the same results were found in many studies [24-27].
This explained by that zinc used in rapid turnover of the skin and loss of zinc through exfoliation. And zinc deficiency may be the original cause of psoriasis. Some studies noted that psoriatic lesions retain a high content of zinc compared with the uninvolved skin, suggesting an imbalance in zinc distribution between serum and psoriatic lesions [24,25]. In fact zinc is a co-factor for DNA- and RNA polymerases required for protein synthesis in involved skin. Lowered level of serum protein or albumin which results from peeling off of a large quantity of scales from the body surface, may be also attributable to decreasing zinc level.
Contradictory to this, some authors found increase level of serum zinc & in some studies the serum zinc was equal in patients and control subjects [24-27].
There was a case report on improvement of psoriatic patient by oral zinc therapy [28].
This approach appears reasonable because copper and zinc are known to be among the constituents of the skin and to play essential roles in maintenance of its function in association with the enzyme systems activated by trace metals. A deficit of those elements may result in the decrease of antioxidant enzyme activity and the increases of oxidative stress induce cell damage [21].
As regard serum copper; in this study increase copper in severe psoriasis than mild and control this is in accordance to many studies [29,30]. Also increase in ceruloplasmin (copper carrying protien) [31,32]. There are several reports stating that the serum copper level is high in psoriasis [33,35]. Copper is present in the serum in at least two fractions: (1) a transport fraction (approximately 5%) loosely bound t albumin; and (2) ceruloplsmin (approximately 95%) firmly bound to globulin. The elevation of serum Copper in psoriasis may be ascribed to an increase in both fractions, especially an increase in ceruloplasmin, a Copper–binding protein,in response to inflammation. Opposite to this finding, a slightly low level of Copper was found in the study done by Lee et al [32] .
Psoriasis may be due to increase oxidative stress and most of trace elements enter in enzymatic process needed for anti oxidants.
Zinc is considered as an antioxidant because the extracellular enzyme superoxide dismutase is zinc- dependent, it plays a vital role in the protection against free radical damage [16].
The disturbance of trace elements not only in the level but also the disturbance in element to element ratio that lead to hemeostatic imbalance which lead to induction and severity of psoriasis [36-38].
Studying the level of trace elements in psoriatic patients gives an idea about the mollecular basis of psoriasis and cytokine etiology.

Our study was limited to a small number of the patients and many studies are needed on a larger numbers of patients to prove the role of trace elements in the pathogenesis of psoriasis.

Conclusion

1. In every patient with psoriasis: it is a must to measure trace element especially calcium, phosphorous, zinc, copper.
2. Correction of trace elements imbalance help in treatment of psoriasis.
3. Further study has to be done in larger population to show the effect of trace elements in psoriasis development and progression.

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