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Effect of Liver Enzymes, Oxidative Stress and Vitamin D3 in Psoriatic Patients

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Abstract

Psoriasis is one of the skin's chronic inflammatory diseases. Psoriasis etiology isn't exactly known. Recently, it has been suggested that the imbalances in oxidant-antioxidant status happening because of the increase in reactive oxygen species production (ROS) and/or deficient function regarding the antioxidant system might be included in psoriasis pathogenesis. The major goal is to evaluate the antioxidant defense status in patients experiencing psoriasis and oxidative stresses represented by malondialdehyde (MDA) level and evaluate liver enzymes and vitamin D3. There are some tests of biochemical parameters and vitamins (GSH, MDA, VitD3, SOD, GPx, CAT, AST, ALT, and ALP) are conducted on 35 patients experiencing psoriasis. The results indicated that the significant increase in MDA in psoriatic patients in comparison to the control at ($P<0.05$), while the level of glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GP_X), and catalase (CAT) decreased significantly in psoriatic subjects compare to control. No significances differences in levels of liver enzymes in psoriatic patients compared to the control group.

Keywords: Oxidative stress, liver enzymes, antioxidant enzymes, psoriasis, and vitamin D.

تأثير أنزيمات الكبد, الجهد التأكسدي و فيتامين د 3 في مرضى الصدفية

مهند سلام مجيد الفياض
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الخلاصة:

الصدفية يمكن ان تعرف كواحدة من امراض المناعة الجلدية الحادة. وبائية الصدفية غير معروفة. وفي الاونة الاخيرة, تم اقتراح ان عدم التوازن بين حالة الاكسدة و مضادات الاكسدة التي تحدث بسبب زيادة انتاج الجذور الاوكسجينية الحرة و أو نقص وظيفة نظام مضادات الاكسدة التي يمكن تضمينها في التسبب في مرض الصدفية. الهدف الرئيسي هو تقييم نظام دفاع مضادات الاكسدة في مرضى الصدفية والجهد التأكسدي المتمثل ب مالون داي الديهايد وتقييم انزيمات الكبد وفيتامين د 3 . هنالك بعض الفحوصات الكيمو حيوية والفيتامينات أجريت على 35 مريض بالصدفية. دلت النتائج على زيادة معنوية في مستوى مالون داي الديهايد في مرضى الصدفية مقارنة بمجموعة السيطرة, بينما مستوى كلوتاثايون, سوبر اوكسايد دسميوتيز , كلوتاثايون بيروكسيديز و

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كاتاليز يقل معنويا في مرضى الصدفية مقارنة بمجموعة السيطرة. لا اختلاف معنوي في انزيمات الكبد في مرضى الصدفية مقارنة بمجموعة السيطرة.

Introduction

Psoriasis is one of the skin's chronic inflammatory diseases. Psoriasis occurs in approximately 3% of the population in the world because there is an increase in the number of patients, also due to the lack of efficient therapies, there is high importance for knowing such disease's precise molecular mechanism. Most recent studies report on psoriasis pathogenesis, it was indicated that oxidative stress (OS) is a risk factor for such dermatosis [1]. OS resulting from an increase in the production of ROS/ RNS as well as a decrease in the activity/concentration of antioxidants which have been accountable for their neutralization [2]. Even though increased ROS were signaling molecules used for regulating the physiological and biological processes, OS was associated with pathologies' myriad. As a redox imbalance state, OS [3], results in oxidative damages in the cellular components (nucleic acids, lipids, and proteins), that might be entailing cellular disorders as well as induce the cell's death via apoptosis [4]. OS is a commonly overlooked and significant point in psoriasis. This multifactorial, complex syndrome was specified via the inflammatory infiltrates' incidence in hyperplasia and abnormally-differentiated dermo-epidermal skin. One of the possible oxidative injury targets is human skin since it has been exposed (in a continuous manner) to the environmental stimuli creating ROS [5]. A lot of conditions, like skin traumas, infections, stress factors and oxidant drugs, might be causing and triggering a psoriasis enhancement. Generally, there is an assumption that psoriasis is one of the systemic diseases besides psoriatic skin involvement. Frequently, it is related to a few pathologies, such as diabetes mellitus, cardiovascular dysfunctions and rheumatoid arthritis, that are referred to as "conditions of oxidative stress" which might per se impose a condition of oxidative stress. It was indicated that there was an inadequate anti-oxidant system in psoriasis pathogenesis, leading to a decrease in antioxidants, compounds that are neutralizing the free radicals [6]. In addition to that, the group related to the main antioxidants identified in the skin involves catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), all belonging to the enzymatic anti-oxidants' group. Along with the enzymatic antioxidants, the non-enzymatic ones like glutathione (GSH), vitamins C and E might be differentiated. It must be highlighted that vitamin E (also referred to as tocopherol) plays a part in creating a physiological barrier; thus, it is the major significant non-enzymatic antioxidant [7]. The inflammation which happens in psoriasis was related to immune cells (adaptive and innate) and the skin cells (fibroblasts and keratinocytes) [8]. Remarkably, ROS intensity in the skin was high compared to the other tissues [9]. Also, oxidative stress is affecting the damaged stratum corneum formation, which was vital in psoriasis [10]. ROS plays a part in the signaling pathways which are induced through TNF-α [11]. Whereas TNF-α is considered to be one of the significant factors in psoriasis pathogenesis, it results in ROS formation in the primary human keratinocytes, leading to more cytokine production [12]. These cytokines such as EGF, IL-10, and IL-4 which are being administered at low-dosage values have decreased the oxidative stress levels in the psoriatic fibroblasts. Yet, such reaction's precise mechanism remains a requirement [2]. There is a possibility that the relationship between ROS and cytokines might be vital in skin disease's pathogenesis, involving psoriasis [12]. The relation between cardiovascular/metabolic diseases and psoriasis is discussed because of the changes in plasma lipoprotein levels. Also, there is a focus on the relation between the levels of the markers specifying the protein as well as lipid oxidation in addition to the oxidative stress level. Furthermore, low-density lipoproteins (LDL) have been identified in the lesional psoriatic skin [13]. Imbalances between the number of antioxidants and ROS result in lipid peroxidation, the development of oxidized fraction LDL (oxidized-LDL) [14], and might cause phospholipase A2 activation. Yet, phospholipase action

is related to arachidonic acid metabolites' formation. Throughout lipid peroxidation, the c-GMP was activated, whereas level of cAMP was decreased, leading to extreme epidermal proliferation in patients experiencing psoriasis [15]. Coherent with previous researches, psoriasis might show potential as well as intrinsic hepatolesivity. Recently, such idea has been supported via first mouse model regarding hepatitis in the imiquimod-induced psoriasis [16]. Also, more and more evidences are suggesting a potential relationship with traditional autoimmune hepatic disorders, including primary cirrhosis or neutrophilic cholangitis [17]. Also, Vitamin D can be specified as one of the oldest hormones in the world, whereas its major source is the skin's exposure to ultraviolet B. Along with the currently well-established advantage in calcium homeostasis, there are very broad vitamin D actions. The receptors of Vitamin D were indicated in many cells such as osteoblasts, enterocytes, parathyroid cells, immune cells, ovarian cells, and keratinocytes [18].

Material and methods

Study design

The study that is being presented was completed at Univ. of Baghdad's College of Science's Dept. of Biotechnology. The study involved 35 psoriatic patients collected from different hospitals in Iraq-Baghdad under the recommendation of doctors who specialize in dermatology and diagnosed with psoriasis, and 35 healthy control. In this research, certain investigations were conducted on serum MDA, GSH, VitD3, SOD, GPx, CAT, AST, ALT and ALP. Samples were gathered, and Chemical Laboratory at Univ. of Baghdad's College of Science, Department of Biotechnology, is where they are being analyzed. In the morning, a 16-hour fast was followed by the collection of blood samples. 5ml of blood samples were drawn from individuals using a syringe and needle.

Determining the serum aspartate aminotransferase (AST) activity:

The activity of the serum AST has been evaluated in a colorimetric method based on Frankle and Reitman, [19] with the use of (Randox), which is a commercially available kit.

Determining the activity of serum alanine aminotransferase (ALT):

The activity of ALT was colorimetrically measured according to Reitman and Frankle [19] utilizing a commercially available kit (Randox).

Determining the activity of serum alkaline phosphatase (ALP):

The activity of the serum ALP has been measured in a colorimetric method at 510nm based on King and Kind [20] utilizing a commercially-obtainable kit (bio-Merieux. France**).**

Determination of serum Vitamin D:

Serum Vitamin D determined through ichroma Kit Human Vitamin D No:INS-VD-EN(Rev.00).

Test principle: The test applies a competitive immune detection approach, a target material in the sample is binding to the fluorescence (FL) labeled detection antibody in the detection's buffer, for creating a complex as sample mix, such complex was loaded for migrating into nitrocellulose matrix, in which covalent couple 25(OH)D3, as well as the bovine serum albumin (BSA), have been immobilized on the test strip, and interference with the binding which is related to target material as well as FL Labeled antibody. In a case when more target materials are existing in the blood, then fewer detection antibodies will be accumulated, causing less fluorescence signal. (this kit and no manual procedure)

Determination of MDA:

Based on Aust and Buege approach, the MDA concentration in serum was concluded Nur *et al*., [21]. The MDA that is created from the breakdown regarding poly-unsaturated fatty acids is serving as a convenient index of the peroxidation reactions. Also, the thiobarbituric acid approach utilized for estimating MDA, which is reacting with the thiobarbituric acid (TBA) provides pink color read at λ max 535 nm [21].

Determination of GSH:

The concentration of serum thiol was estimated based on Ellman assay approach [22].

Determination of SOD activity:

The SOD activity assay kit (Colorimetric) (ab65354) has been considered a sensitive and robust kit to measure the activity of SOD in tissue/cell lysates, plasma, serum, as well as other biological fluids. Such SOD's inhibition activity has been evaluated through colorimetric technique at OD 450nm.

Determination of GPx assay:

GPx Assay Kit (Colorimetric) (ab102530), GPx will be reducing the cumene hydroperoxide, whereas oxidizing the GSH to glutathione disulfide (GSSG). Also, the created GSSG has been decreased to the GSH with the consumption related to NADPH through glutathione reductase (GR). NADPH reduction (simply evaluated at 340 nm) has been proportional to the activity of GPx.

Determination of serum catalase (CAT) assay:

Catalase Activity Assay Kit (Colorimetric/Fluorometric) (ab83464) has been direct, simple, extremely sensitive assay to measure the catalase activity in various biological samples like tissue and cell lysates or biological fluids. Concerning the discussed assay, catalase that exist in the sample will be reacting with hydrogen peroxide (H_2O_2) for producing oxygen and water. Also, unconverted H_2O_2 will be reacting with the probe for producing a product which might be calorimetrically measured at OD570nm or fluorometrically evaluated at Ex/Em = 535/587nm. (this kit and not a manual procedure)

Statistical analysis:

Data analysis has been achieved with the use of SPSS for Windows, V22 (SPSS Inc. Chicago, Illinois, United States). The test of Bonfferoni Post Hoc concerning multiple comparisons have been utilized following the ANOVA tests. [23].

Results and discussion

Overall, there are 35 patients experiencing psoriasis are recruited for the presented work. The values of oxidative stress and vitamin D3 in control patients and psoriatic ones are shown in (Table1).

Table 1: Levels of VitD3, GSH, and MDA in psoriatic patients.

Parameters	Control subjects (n=35)	Psoriatic subjects (n=35)	P value
MDA (µmol/L)	1.27 ± 0.22 a	3.11 ± 0.67 b	<0.05
GSH (µM/mL)	4.97 ± 0.37 a	2.88 ± 0.97 b	<0.05
S.VITD3 (mg/L)	22.67 ± 3.76 a	14. 87 ± 1.37 b	<0.05

Value mean ± standard error, a different letter (a, b) significant different ($p<0.05$). b represented a significant difference with control (a).

The presented study investigated the involvement degree of a few biochemical parameters in the complications related to psoriasis. MDA, GSH, and VitD3 were examined. An increasing level of MDA in psoriatic patients ($p < 0.05$) compared with control subjects, while the decreased level of GSH and VitD3 in psoriatic patients compared with healthy subjects.

The data provided by this study are in accordance with three researches patients experiencing psoriasis found considerably low Vitamin D concentrations in patients experiencing psoriasis in comparison to the controls [24-26]. Vitamin D3 is participating in the differentiation process and keratinocyte growth, also impacting the immune functions related to T-lymphocytes and dendritic cells, have the ability to inhibit the production of IL6 and IL2, that might be responsible for the fact that the vitamin D levels have been changed in patients experiencing psoriasis [27]. Yet, one of the large population based studies with 5,693 controls and 148 psoriasis identified no differences in the concentrations of vitamin D between both groups [26]. In addition, vitamin D has a lot of functions in the skin such as inhibiting proliferation as well as promoting the keratinocytes' differentiation, modulating the cellular and humoral immune system along with participating in the hair cycle. Those actions are occurring because of the vitamin D binding in their receptors that exist in the keratinocytes. In turn, such cells have the ability to produce vitamin D which is acting on receptors in autocrine action. Vitamin D's significance in psoriasis might be shown via excellent therapeutic responses to the vitamin D analogues typically utilized to treat such disease including calcipotriol. Some of the published researches specified that vitamin D might be acting on the immune system through the inhibition of significant cytokines for Th17 and Th1 differentiation which were vital pathways in psoriasis pathophysiology [28].

The increase in the production of ROS throughout the inflammatory process in psoriasis, due to inadequate antioxidant mechanisms, might be increasing lipid peroxidation. About cell membranes, such a process might be resulting in cell damage via continuing in the chain reaction. Also, it is accountable for the phospholipase A2 activation, generating various mediators through arachidonic acids, as well as deactivation related to adenyl cyclase and the guanylyl cyclase' activation cause a reduction in the ratio of cAMP/cGMP, which is accountable for the epidermal hyperproliferation [29]. An increase in ROS or free radicals' production results in oxidative damage to the biological molecules, tissues and cell membranes. Besides, ROS induced oxidation related to the poly-unsaturated fatty acids in biological systems leading to the development of lipid peroxidation products like malondialdehyde (MDA). High platelet, tissue, erythrocyte, plasma and serum levels of the MDA, further plasma lipid-peroxidation products, along with an association with the severity of the disease were indicated in the patients previously experiencing psoriasis [30]. The presented work identified a statistically significant high level of MDA in patients experiencing psoriasis in comparison with the controls.

Effects of antioxidant enzymes in psoriatic patients

The activity related to all antioxidant enzymes in the patients experiencing psoriasis has been significantly low (P less than 0.05) compared with that of controls (Table2). Serum GPx, CAT, and SOD activity levels have been identified as being significantly decreased (P less than 0.05) from mild to moderate as well as from moderate to severe psoriasis patients. The reduced serum antioxidants enzyme activity levels are negatively correlating with psoriasis severity.

Table 2: Levels of antioxidant enzymes in psoriatic patients.

Parameters	Control subjects (n=35)	Psoriatic subjects (n=35)	P value
SOD (µU/ml)	22.45 ± 0.67 a	16.43 ± 0.97 b	<0.05
GPX (nmol/ml)	45.32 ± 0.85 a	33.56 ± 0.96 b	<0.05
Catalase (nmol/ml)	14.89 ± 0.44 a	9.54 ± 1.27 b	<0.05

Value .represent mean ± standard error, a different letter (a, b) represent asignificant different ($p<0.05$).

Psoriasis can be specified as one of the recurrent inflammatory skin disorders, categorized via significant increase in keratinocyte proliferation and abnormal differentiation. Lately, many studies were focusing on oxidative stress and its association with psoriasis. It has been suggested that oxidative stress plays a part in psoriasis pathogenesis [31]. Gutsze and Gornicki, [32] identified that the concentration of MDA has been increased, while the activity related to antioxidant enzymes CAT and SOD have been reduced in the psoriasis patients' erythrocytes in comparison to the control subject [33]. Research that has been carried out by Rocha *et al*., [31] examined the oxidative stress related to patients experiencing psoriasis in correlation with the disease severity. The researchers specified considerably increased concentrations regarding plasma MDA, correlating positively, and low concentrations of VitA and VitE negatively correlating with the psoriasis severity. Decreased antioxidants concentration and increased oxidants concentration results in oxidative stress indicating lipid-peroxidation. This could result in cell damage through continuous chain reactions. Also, it might be accountable for the activation of phospholipase A2, the formation of various mediators through the arachidonate, deactivating of the adenylate cyclase as well as activating the guanylate cyclase resulting in a reduction in the ratio of cAMP/cGMP accountable for epidermal proliferation [34]. Yet, one can frequently find information related to SOD levels in the epidermis of individuals experiencing psoriasis. The analyses specified a reduction in SOD levels in psoriatic keratinocytes. Following utilizing an antioxidant supplementation, a restoration in the antioxidant enzyme's levels might be indicated corresponding to a healthy condition [35].

Effect of liver enzymes in psoriatic patients

Liver enzyme levels in psoriatic patients weren't significantly different (P more than 0.05) compared to the control group (Table3).

Table 3: Levels of liver enzymes with psoriatic patients.

Parameters	Control subjects (n=35)	Psoriatic subjects (n=35)	P value
AST (U/L)	28.0 ± 0.22	26.5 ± 0.45	> 0.05
ALT (U/L)	31.0 ± 0.45	29.3 ± 0.87	> 0.05
ALP (U/L)	180.0 ± 1.33	188.65 ± 0.77	> 0.05

Value .represent mean ± standard error.

The data of this study indicate no significant difference in the liver enzymes in Iraqi patients experiencing psoriasis, even though a few such patients were taking treatment. The results of this work are not in accordance with a few other studies, idiopathic liver biochemistry disturbances in psoriasis aren't entity well-described in the literature. A research that has been carried out by Tula *et al*., [36] reviewed (retrospectively) a total of 518 psoriasis patients, and of those the liver biochemistry disturbances as well as a possible association with the majority of risk factors (diabetes mellitus, obesity, hepatotoxic medications, alcohol consumption, infectious hepatitis, and dyslipidemia) have been assessed [36]. An increase in the liver

enzymes has been specified to be idiopathic in the patients with no recognized risk factors: 4% of mild-moderate as well as 8% of a severe increase in tests of liver function [36]. Yet, in our opinion, the percentage (4–8%) might not be considered idiopathic since the authors (for retrospective study nature) didn't assess every potential cause of hyper-transaminasemia (celiac disease, autoimmune disorders, Wilson's disease, and Hemochromatosis) [36].

The bridge between the liver and skin starts to delineate, while psoriasis might be one of its pathognomonic examples. Indirectly, the liver might be affected via psoriasis, a massive consideration of the liver profile was vital. According to guidelines, the majority of exclusively psoriatic patients undergoing systemic therapies were checked (routinely) for liver affections. Lastly, the main aim of this study is to underline the wide spectrum of the diseases of the liver which might co-occur in psoriatic patients and secondary suggest a routine liver check in psoriatic patients with no systemic therapy-psoriasis related. Besides the important role of adipose tissue in mediating the interplay between skin and liver, (severe) psoriasis may have a direct impact on liver disease, possibly via mechanisms beyond overweight and obesity [37] In a biological system, oxidative stress is said to occur due to the physiological imbalance, when the antioxidant defense system is overwhelmed by the excessive presence of reactive oxygen species (ROS) and free radicals [38]. As a result of an imbalance between ROS and antioxidant defense, the consequent damage to potential cellular functions leads to various pathophysiological alterations in the liver [39]. Several *in vitro* and *in vivo* studies have reported that free radicals especially, ROS intervene and modulate various cellular functions *i.e.*, cell cycle, signaling, adhesion, metabolism, and death [40]. Hepatocytes are well equipped with non-enzymatic and enzymatic protective systems that play a significant role in nullifying free radicals. Superoxide dismutase **(**SOD) is the "first line" enzyme of defense in an antioxidant system that plays a major role in scavenging superoxide radicals formed during oxidative damage. Although most studies indicate the relationship between oxidative stress represented MDA and antioxidant system represented GSH, SOD, GPx, and CAT, with liver disease represented liver function represented AST, ALT and ALP, and psoriasis literature is known with its correlation with oxidative stress, so in our study we ran a test of liver function on psoriatic patients, but we get on no significant difference in liver function with Iraqi psoriatic patients.

Conclusion: The present study concludes that there is a relationship between vitamin D and enzymatic antioxidants and non-enzymatic antioxidants (GSH) and there is an increase significance in oxidative stress represented by MDA, and a decrease of enzymatic and non-enzymatic antioxidants in psoriatic patients. Also, there is a decreased significance in VitD3 in psoriatic patients compared with healthy control. In addition to this work conducted no significant differences in liver enzymes in psoriatic patients.

Ethical clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental health and higher education and scientific research ministries in Iraq.

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