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Long term exposure to skin scabies infection may induce a secondary autoimmune psoriasis disease in patients live at southern area in Iraq

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Abstract:
This study aimed to understanding the relationship between scabies and psoriasis, therefor some immunological, hematological and immunobiochemical tests were investigated in scabies patients and scabies-psoriasis patients then compare with control. This study was achieved in the southern marshes of Iraq were the most population was suffering from scabies disease, 57 scabies patients were included, they were divided into two groups scabies patients: (32, male: 13 and female:19) and scabies-psoriasis (25, male: 15 and female:10) also 20 cases control were included. All cases were serologically positive for anti-*Sarcoptes* IgG. Immunological, hematological and immunobiochemical tests were investigated in all groups then compare with control.The result show that Scabies incidence infection was highest in children (8-16 years), female represents the highest ratio in scabies patients. A higher significant level in scabies-psoriasis patients were found for C3,C4, but IgG, IgA, IgE, IL-5, IL-6 and IL-10, IL-18 and IL-1β, TNF-α, and IFN-γ were higher significant in both groups, IgM was found to be increased with significant level in scabies patients and decreased in scabies-Psoriasis patients, SOD activity have higher significant differences in scabies patients but lower significant in scabies-psoriasis also the MAD level.In conclusion of this study, some scabies patients make development of other secondary immunological disease (psoriasis) upon prolong infection, particularly in patients whom not use any treatment.
Key words: scabies, psoriasis, autoimmune disease, antioxidant activity

Introduction:

Scabies is a disease causing an infestation of the human skin by the human *Sarcoptes scabiei* var. *hominis*, the upper layer of the skin burrows by scabies mits, where it lives then lays its eggs. intense itching and a pimple-like skin rash are The most important symptoms of scabies. Direct prolonged, skin-to-skin contact with a person who has scabies consider the usually method for transmission. All ages and races in the worldwide are strikes to scabies, under crowded conditions Scabies can be spread rapidly in present of close body contact. In the worldwide its estimated almost three hindered million cases occur annually [1]. People who are very clean and neat can get scabies. It tends to spread easily in nursing homes and extended-care facilities. Approximately hundreds to millions of mites can infest the host, that usually child, elderly and immune compromised [2]. Scabies if it is not treated on time it can definitely get worse, many complications caused due to this because it lets

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many other infections to the body and prolong the treatment. Severe dermatitis or psoriasis can be confused with Crusted scabies, so crusted lesions appear as a thick and hyper keratotic scales over the knees, palms, elbows, and soles, when suspected dermatitis or suspected psoriasis, do not respond to treatments then the diagnosis of crusted scabies can be considered [3]. Continuous scratching may result into opening of sores on the skin and invite bacteria to penetrate. a complicated stage of scabies mostly occur after a secondary bacterial infections. Staphylococcus a ureus infection is an important causal organism of the bacterial infections, which leads to reddening of skin, blisters formation and spores, which acquired yellowish-brown color at a later stage, filled with pus and very painful. At an extreme stage, it is known to cause kidney- inflammation as well. Scabies have relationship with secondary complications, such as acute post-streptococcal glomerulonephritis and rheumatic heart disease [4]. The development of serious downstream systemic will occurred if these secondary complications left untreated then cause life-threatening conditions [5]. Psoriasis or sever dermatitis could be confused with the crusted scabies. Knees, palms, elbows, and soles crusted lesion when appear as thick and hyperkeratotic scales a suspected dermatitis or psoriasis can be considered, do not respond to treatment the diagnosis would be shifted to crusted scabies[6].Psoriasis is not contagious. It is a chronic type of autoimmune skin disease in which the body immune system will attack itself leading to the rapid build-up of the skin cells which result scaling on the skin's surface [6].In addition to that the scabies disease induced oxidative stress, oxidative stress are imbalance between the antioxidant levels and reactive oxygen species[7- 12]

Material and methods:

This study was achieved in the southern marshes of Iraq at Thie-Qar governorate (from March 2014 to April 2016) in which most of the population was suffering from scabies disease, particularly in children for long duration. The patients were very poor and don't use any treatment which make them a good case for study. Fifty seven scabies patients were included in this study, they were divided into two groups: (scabies patients:32, male:13 and female:19), (scabies-psoriasis:25, male:15 and female:10) also 20 cases control were included. All diseased patients were diagnosed by testing IgG antibodies against "*Sarcoptes scabiei* in serum (ELISA, Afosa GmbH, Dahlewitz/Berlin,Germany)", all cases were serologically positive for anti-*Sarcoptes* IgG. All information regarding; age; gender ; time of onset of scabies and other information were recorded. Immunological, immunobiochemical and hematological tests were achieved using patients venous blood. Serum IgA, IgG and IgM and complement components C3 and C4 were measured using radial immunodiffusion (RID Kit, LTAonline, Italy).IgE level measured by using enzyme linked immunosorbent assay (IgE ELISA Test Kit, Genzyme, CA, USA). "Turbidimetric Kit" with High-sensitivity for C-reactive protein in plasma with specific high-sensitivity methodology (BioTécnica, Brazil)" was used , Serum TNF-α, IL-6, IL-10, IL-5, IL-1β, and IL-18 levels were determined using ELISA kits (R&D Systems, Shanghai, China). Differential count was performed by using "CYAN Hemato analyzer automatic hematology analyzer" (Catalog No. CY006. Diagnostic , Langdorpseteenweg160,B3201Belgium).

Statistical analysis

Data are described as the mean±SD, SPSS17 program was used for statistical analysis, Statistical significance was at (P<0.05), so that data was considered statically significant when p-values were less than 0.05.

Results :

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Depending on age, the infected individuals were divided into three groups (table-1). Scabies incidence infection was highest in children (8-16 years), while the highest level for scabies-psoriasis incidence was seen in age group(41-53 years).

Table (1): Age distribution of scabies in all groups

Age (years)	Scabies n=32	Scabies-psoriasis n= 25
8-16	22	0
17-26	5	3
27-40	3	6
41-53	2	16

According to the gender, female represent the highest ratio in scabies patients, while in scabies-psoriasis patients male shows the highest ratio as shown in table (2).

Table (2): Gender distribution in all groups

Scabies n=32		Scabies-psoriasis n=25	
Male	Female	Male	Female
13	19	15	10

Complement play an important role in estimation of psoriasis disease, level of C3 and C4 was measured in this study. The results showed a higher significant level in scabies- psoriasis patients (C3: 130.64±30.2 and C4: 35.82±25.3) compared to control (98.26±24.1, 26.62±5.61) respectively. Also another parameter was estimated (hs-CRP) and the results of both groups was higher significant (4.3 ± 0.4, 5.35±0.6) compared to control (Table-3).

Table (3): level of some immunological parameters (complement and CRP) in all groups

Parameters	Control n=20	Scabies n=32	Scabies-psoriasis n=25
hs-CRP(mg/L)	2.1±0.4	4.3 ± 0.4	5.35±0.6
C3 (mg/dL)	98.26±24.1	100.3±81.3	130.64±30.2
C4 (mg/dL)	26.62±5.61	27.4±18.2	35.82±25.3

The result describe as Mean±SD, significant at ($P < 0.05$)

Immunoglobulin level was also measured in this study. The results of immunoglobulin level showed IgG was higher significant in both groups (1623.81±98.1,1991.50±67.2 mg/dl) respectively as compare with control (1100.50±67.2). IgM was found to be increased with significant level in scabies patients (200.8± 14.3 mg/dl) and decreased in scabies-Psoriasis patients(129.1±76.8) compared to control value. IgA and IgE values also showed a higher significant level in both patients with scabies and scabies-psoriasis(208.8± 20.4, 210.1±12.7mg/dl)(0.063± 0.02, 0.064±0.12 mg/dl) respectively compared to control levels (Table-4).

Table-(4): Serum immunoglobulin levels in normal controls and patients with scabies and scabies-psoriasis patients.

Parameters	Control n=20	Scabies n=32	Scabies-psoriasis n=25

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IgG (mg/dL)	1100.50±67.2	1623.81±98.1	1991.50±67.2
IgM (mg/Dl	130.1±76.8	200.8± 14.3	129.1±76.8
IgA (mg/dL)	119.9±12.7	208.8± 20.4	210.1±12.7
IgE (mg/dL)	0.028±0.02	0.063± 0.02	0.064±0.12

The result describe as Mean±SD, significant at (P <0.05)

Other immunological parameters were also investigated in this study (Table-5). The research results showed a significant level in IL-5, IL-6 and IL-10 (7.4±1.4, 7.8±2.1(pg/ml), (69.98±34.1, 73.25± 47.3(pg/ml) and (1.23±1.2, 0.15±1.46 (pg/ml)) in both scabies and scabies-psoriasis diseases respectively compared to control. IL-18 and IL-1β markers were also measured and the results showed significant values in both parameter (114.93±3.48, 128.4 ± 13.8(pg/ml) and 39.94±1.12, 38.44±1.5 (pg/ml)) in both scabies and scabies-psoriasis diseases respectively compared to control. Another inflammatory parameters which are TNF-α and IFN-γ were measured in this study and the results showed also there is a significance values in both diseases (scabies and scabies-psoriasis) compared to control (table-5) .

Table-5: Correlation between clinical assessment of some serum immunological markers in normal control and in patients infected with scabies and scabies-psoriasis disease.

Parameters	Control n=20	Scabies n=32	Scabies-psoriasis n=25
IL-5 (pg/ml)	4.2±2.4	7.4±1.4	7.8±2.1
IL-6 (pg/ml)	3.58 1.34	69.98±34.1	73.25± 47.3
IL-10(pg/ml)	0.92±0.56	1.23±1.2	0.15±1.46
IL-18(pg/ml)	55.6±2.5	114.93±3.48	128.4 ± 13.8
IL-1β(pg/ml)	8.9±5.2	39.94±1.12	38.44±1.5
TNF-α (pg/ml)	21.84± 6.34	126 ±22	261.5±96.1
IFN-γ (pg/ml)	15.0±4.2	66.1±16	73.2 ±4.1

The result describe as Mean±SD, significant at (P <0.05)

Table (7) showed that the Superoxide dismutase **(**SOD) activity have higher significant differences in scabies patients (0.08±1.07), but lower significant differences in scabies-psoriasis (0.01±0.12) as compare with control. Level of MAD was lower significant in scabies-psoriasis (2.19±0.34) as compared to control.

Table (7): Mean± SD for oxidation parameters in all study groups

Oxidative stress Parameters	Control n=20	Scabies n=32	Scabies-psoriasis n=25
SOD Activity %	0.01±0.006	0.08±1.07	0.01±0.12
MAD(nmol/ml)	2.24±0.36	2.26±0.56	2.19±0.34

SOD: Superoxide dismutase MDA: Malonaldehyde

Discussion:

The incidence of scabies in this study reported to be higher in children than in adult and in elderly patients, also more common in female than in male, while in elderly patients the incidence of scabies-psoriasis infection was higher compared to young adult and children such results was reported by Root. Et al.[1]who founded scabies disease incidence is more in female than in male and more prevalent in children and young adults than in elderly

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patients. C3 and C4 parameters were investigated in this study and the results demonstrated no differences between scabies patients and control.

hs-CRP was elevated in scabies-psoriatic patients when compared with control and the difference was statistically highly significant (*P* value 0.05), but the level was similar to that in scabies patient, the role of CRP is investigated by several studies, in psoriasis pathogenesis, our result agree with Kimball *et al*.[2] and Coimbra *et al*.[3]. In a study by Kimbell *et al*., CRP levels changing according to presence and severity of disease, CRP levels higher in patients with increasing disease severity but lower in control [2]. Thus, these results may be because the increase in inflammatory response, so that patients have two disease scabies then develop psoriasis. other studies have also documented a correlation between increased levels of CRP and disease severity [4]. C3 and C4 levels were significantly increased In the patients of scabies-psoriasis as compare with both control and scabies only. C3 and C4 level in many reports were variable for psoriasis patients. Researchers in some studies suggested, that C3 and C4 have significant increase in psoriasis patients, as comparison to control [5]. But in one study there is increase in level of C3 also decreased in C4 levels in psoriasis patients [6]. It is documented that the complement cascade activities by attachment of IgG and IgM antibodies with a pathogen, then give strong for activities of these antibodies, Scabies-Psoriasis patients, have higher significantly levels of all immunoglobulin in this study, as compare with control, but there is no significant differences for IgA and IgE in Scabies-Psoriasis patients as compare with scabies patients. IgM shows lower significant differences in scabies-psoriasis patients as compare with scabies only, while IgG shows higher significant differences as compare with scabies only. Psoriasis patients have increased levels of IgA and sometimes IgG, which found in the layer stratum corneum of the skin, this action may be give stimulation for attract neutrophils and complement [13] in this present study, the results demonstrated that total serum IgE significantly increased, in scabies-psoriatic patients as comparison to control, this agreement with results of Chen *et al*. [14] but disagree with Mutevelic-Arslanagic, *et al*.,2000 [15]. We didn't found any study deal with scabies-psoriasis patients. Some other documented , that the Skin defense mechanisms are important, skin disorder pathogenesis is caused by abnormal immune reactions, such as eczema, dermatitis, also psoriasis, the Scabies effect on the Keratinocytes, make it produce over-expression, of different pro-inflammatory cytokines, then develop psoriasis, keratinocytes in psoriasis patients, then make production and release IL-1, IL-6, IL-15, IL-18 and IL-20, which responsible for development of psoriasis [16]. All cytokines in present work (TNF-α, IFN-γ, IL-6, IL-1β, IL-18, IL-10 and IL-5) have higher significant differences in scabies-psoriasis patients as compare with control and scabies only. Abnormal T-cell, involvement in generating the symptoms of psoriasis, although T cell can divided according to their cytokines, into Th1 cells, which often secrete IFN-γ, IL-2, and TNF-α, and support cellular immunity, In the other hand Th2 cells produce primarily IL-4, IL-5, and IL-10, and responsible for B cell proliferation, also responsible for antibodies production [17]. The imbalance between Th1 and Th2 cell, may causing development of different autoimmune disorders, Some study have found high levels of some cytokines in psoriatic patients, whereas others have not found [18]. The pathogenesis of psoriasis, is a multistep process, and many kinds of cytokines has an important role in these processes [19]. The cytokines IL-2 and IFN-γ, are secreted by Th1 activation, these cytokines activate by some way,a large group of immune related genes, so that contribute to the all pathogenic process [20]. Our result indicated that Th1 cytokine IFN-γ were elevated in the sera of scabies-psoriatic patients, so, support the hypothesis that "Th1 cells may play important role, in the pathogenesis of disease"[21]. Ozer Arican *et al* and Abanmi *et al*. documented, increase levels of TNF-α compared with controls [22], this in agreement with our results. While Jacob E *et al*.2004,

demonstrated there is no difference in the level of TNF-α in patients and controls [23]. The cytokine TNF-α play important roles in the psoriasis pathogenesis, including; stimulation, immune responses of skin, epidermal growth, and vascular proliferation, It is believed that TNF-α works as synergistic, with other cytokines to induce the pathogenesis of psoriasis [24]. Some study documented that the development of psoriasis, depends on the presence of TNF-α, many studies have suggested, a significant elevation of TNF-α in serum and skin lesion in psoriatic patients, compared with the controls [25]. Also, others suggested, that the removal of the TNF–α of serum, will cause decrease in T cells numbers, also cause reduction in the epidermal hyperplasia in patient with psoriasis [26]. Our result suggests, that the induction, and maintaining of psoriasis, causing by overexpressed Th1 cytokines, like IL-6, IFN-γ and TNF-α. Some others have demostrated, that the proteins of scabies mite play an important very complex role, in the immune response of host skin, through make changes in production of chemokine and cytokine, so that expression of adhesion molecules from fibroblasts, keratinocytes and endothelial cells [26]. Some study documented presence of components which are unknown in the whole mite extracts (S. scabiei var. canis), which down regulate production of IL-8 and IL-1ra , also stimulate the production of VEGF and IL-6 in normal epidermal keratinocytes which cultured, in the similar study, IL-6, IL-8, G-CSF also VEGF were up regulated in culture contend normal dermal fibroblasts of human [27]. Although, these result, confirm unknown proteins of mites have properties for immunomodulatory, which cause invasion for the host, via down regulating, or depressing of inflammatory processes in skin cell, result in a delayed immune reaction. Some reports documented, that the stimulating of human keratinocytes occur by proteolytic activity of house dust mite (HDM), cysteine and serine proteases, then cause regulating IL-8 production in vitro [28]. It is demonstrated that the scabies mite and cysteine and serine proteases have specific effect, homologues to the HDM cysteine protease group, one and three allergens [29]. The effect of scabies mite homologues to HDM allergens on the immune system of skin, by some study is unknown, these include a scabies mite "mu class and a delta class glutathione S-transferase group 8 allergen implicated as a major allergen in scabies immune response" (30-31). There is increase in the level of IL-6 in scabies-psoriasis patients, this result agree with some studies by Koliadenko *et al* and Abanmi *et al*., [32]. In the other hand Jacob *et al*. documented no difference in IL-6 levels in serum [33]. The cytokine IL-6, have many roles, including mediates T-cell activation, stimulates proliferation of keratinocytes, also it mediates the acute phase responses [34]. The present study result of higher IL-6 levels in scabies-psoriasis patients are consistent with the important role of IL-6 in the psoriasis pathogenesis. Serum levels of IL-1β was not increased in scabies-psoriasis patients, but in other study shows higher levels of IL-1β, in blister fluid than in serum, this observation supporting the hypothesis, that the IL-1β is locally produced in psoriatic lesions [35]**.** The interactions between T cells, dendritic, neutrophils, also keratinocytes, and proinflammatory cytokines, which produced, by these cells (TNF-α, IFN-γ, IL-17, IL-22, IL-23, IL-12 and IL-1β), participate in the initiation of psoriasis cutaneous inflammation characteristic [36]. The expression of MHC class I on keratinocytes, induce by IFN-γ, MHC class I may induce the present of putative auto antigens, to intra epidermal T cells, which causing high activation of pathogenic autoimmune T-cells [37]. Some study reported that the Psoriasis patients, have increased expression of IL-18 in the skin tissue and blood [38,39]. The IL-18 is considered a biomarker, for the severity of psoriasis [40]. Its demonstrated that in cellular adhesion IL-18 have an important role, so it the final pathway, using by TNF-*α* and IL-1 that leads to expression of ICAM-1 (intercellular adhesion molecule 1) (41). expression of receptor of IL-18, is up regulated by IL-12, the two cytokines acting in synergize to cause stimulation the release of IFN-*γ* [42]. The IL-18 improved, that have important action on dendritic cells

accompanied by IL-12, the tow cytokines greatly increase IFN-γ production [43]. some reports supported the role of TNF-α and IFN- γ in the clinical manifestation of psoriasis, Similar to other inflammatory diseases [44]. Products of neutrophil activation were confirm to be higher in the serum of patients with psoriasis [45]. Usually neutrophils are increased in psoriasis patients, Because of the increasing which occur in level of plasma CXCL8 (neutrophil chemotactic factor), in psoriasis patients, [46,47].In this study ,there was increase in MDA level and decrease in SOD activities in scabies disease as compared to control group. MDA is indicator of oxidative stress[48-56] .

Conclusion:

The results of this study suggested that prolonged and repeated infection with *sarcoptic scabies* parasite that lead to production of scabies disease. Such infection will stimulate both humeral and cell mediated immunity, activation of macrophages, increased complement production, cytokine secretion and antibody production , that interned lead to development of other secondary diseases. After development of these diseases in scabies patients the immune response to the scabies parasite will decreased (host tolerance to parasite antigen) and the immune response will shifted toward the new disease in spit scabies disease still exist.

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