# The Effect of Pioglitazone on Matrix Metalloproteinase-9, Matrix Metalloproteinase-2, Tumor Necrosis Factor-α, Vascular Endothelial Growth Factor and E-Selectin in Skin Lesions in Psoriatic Patients with and without Psoriatic Arthritis

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## Abstract

**Background:** Psoriasis is a common inflammatory skin disease characterized by infiltration of inflammatory cells into the epidermis and altered keratinocyte differentiation. The aim of the present study was to investigate the role of MMP-9 in the development of psoriasis by assessing the presence of MMP-9 in lesional skin and in sera of psoriatic patients with & without psoriatic arthritis, the association of MMP-9 with the activity of the disease, the relationship between MMP-9 and TNF-α production as well as to evaluate the effect of pioglitazone (one of the agents thiazolidinediones) on TNF-α, MMP-9, MMP-2, VEGF and E-selectin production and in treatment of psoriasis.

**Subjects and Methods:** Thirty-five psoriatic patients (28 males, 7 females) were included in this study. They were divided into 2 groups. Group I (PsA) included 15 psoriatic patients, clinically presenting joint symptoms associated to the cutaneous disease (PsA). Group II (Ps) included 20 psoriatic patients, clinically presenting cutaneous disease without psoriatic arthritis (PsA). Each psoriatic patient received pioglitazone 30 mg/day orally for 10 weeks. Lesional tissue specimens were taken, in the same skin area before and after 10 weeks pioglitazone treatment. Tissues were kept in short term cultures and production soluble mediators such as TNF-α, MMP-9, MMP-2, VEGF and E-selectin, which include angiogenic molecules associated to the development of plaque psoriasis, were measured in the culture supernatants by ELISA. MMP-9 concentrations were also measured in the sera. The cutaneous activity of disease was evaluated by the Psoriasis Area and Severity Index (PASI).

**Results:** Clinical and laboratory assessment indicated that all patients had a significant improvement of the PASI score after 10 weeks of pioglitazone therapy. The clinical improvement was associated to a significant decrease of TNF-α, MMP-9, MMP-2, VEGF& E-selectin levels (P< 0.05) , spontaneously released by lesional biopsies before and after therapy. A significant decrease of MMP-9 (P< 0.01) in the sera, associated to the clinical improvement was also found. In addition, significant positive correlations (P< 0.01) were found between the TNF-α and PASI score, MMP-9, MMP-2, VEGF& E-selectin (r=0.85, 0.84, 0.58, 0.63, 0.67 respectively), as well as between the MMP-9 and PASI, MMP-2, VEGF& E-selectin (r=0.82, 0.39, 0.69, 0.41 respectively) of patients with PsA after pioglitazone treatment. In psoriatic patients without psoriatic arthritis after pioglitazone treatment there were also significant positive correlations between the TNF-α and PASI score ,MMP-9, MMP-2, VEGF& E-selectin(r=.0.87, 0.68, 0.53, 0.61, 0.51 respectively), as well as between MMP-9 and PASI, MMP-2, VEGF& E-selectin (r=0.95, 0.51, 0.58, 0.45 respectively).

**Conclusion**: The current study shows the existence of a direct relationship between MMP-9 and TNF-α production strongly suggesting that MMP-9 may play a key role in the skin inflammatory process. Our findings also demonstrated that pioglitazone could be considered as an efficacious and safe agent for the treatment of psoriasis. The optimum dose and duration of pioglitazone therapy remain to be determined.
**Key words**: Psoriasis . Psoriatic arthritis . Matrix metalloproteinase-9 . Pioglitazone

## Introduction

Psoriasis is a chronic inflammatory skin disease characterized by hyperproliferation of epidermal cells with prominent blood vessels and a thick perivascular lymphocytic infiltrate (Camp, 1998). Epidemiological data demonstrate an association with a number of distinct disorders of the joints (psoriatic arthritis), the intestine (Crohn's disease), and skin (pustular disorders), as well as increased risk of cardiovascular disease (Christophers, 2006). The etiology of psoriasis is still unknown. Whether the disease results from a primary abnormality in epidermal keratinocytes or depends upon a deregulation of the immune system it has been matter of controversial debating (Bos& De Rie., 1999). Recent evidence, however, indicated that activated lymphocytes and keratinocytes are both required for the development of psoriatic lesion (Sano *et al.,* 2005). In fact, the chronic, self-aggressive, epidermal T cells activation, characteristic of the disease, might be initiated by common streptococcal infections (β-haemolitic streptococci) that, in turn, might trigger a cross immune recognition between streptococcal M proteins and those keratins that are pathologically up-regulated in psoriatic lesions (Johnston *et al*., 2004). Psoriasis is currently thought of as a T-cell mediated 'Type-1' autoimmune disease. Gene expression changes in psoriasis lesions have been well documented, and strongly support an important role for tumor necrosis factor and interferon gamma signal pathways in its pathogenesis. The strongest genetic determinant of psoriasis identified to date lies within the class I region of the multiple histocompatibility locus antigen cluster, although its low penetrance implicates a requirement for other genetic risk factors. Multiple genome-wide linkages and an increasing number of association studies have been carried out, leading to multiple linkage peaks, and the identification of potential low risk variants. A number of these variants lie within genes encoding components of the immune system. However, the functional relationships between predisposing genetic variation are unclear, and presumably involve genetic

susceptibility factors affecting both immune cell activation and keratinocyte differentiation. The interaction of environmental trigger factors with genetic effects is also not understood, but provides further evidence for the complex basis of this disease (Shiina *et al*., 2004 & Liu, *et al.,* 2006). An auto-immune response may thus be sustained by a mechanism of molecular mimicry. Indeed, psoriatic keratinocytes exhibit an altered phenotype characterized by a costitutive Stat3 activation (Sano *et al.*, 2005) and a different response to IFN-γ compared to normal keratinocytes ( Nickoloff *et al.,* 1989 & Wrone-Smith *et al.,* 1997).

About one third of patients with psoriasis also suffer of an inflammatory arthritis with clinical and biological features that are partially similar to rheumatoid arthritis (RA) (Gladman & Rahman, 2001). Although, the systematic classification and the diagnostic criteria for this form of arthritis are still under validation (Helliwell & Taylor, 2005), psoriatic arthritis (PsA) has been recognized as a clinical entity distinct from RA, due to the absence of the rheumatoid factor as well to the presence of specific clinical features. Articular erosions in PsA occur less commonly than in RA and progression to joint destruction occurs at a slower rate; nevertheless it can lead to disability(McHugh *et al*.,2003).

Compelling evidences indicate that TNF-α plays a central role in sustaining the psoriatic inflammatory process in skin as well as in joints (Kane &Fitzgerald, 2004). In psoriatic skin, TNF-α is the prevalent cytokine, it can be produced by several cell types including activated T cells, keratinocytes, macrophages and Langerhans cells (Lockslay *et al*., 2001). Moreover, in epidermal keratinocytes, TNF-α regulates genes involved in immune and inflammatory response, including those involved in cell motility or cytoskeleton changes or in extracellular matrix remodeling (Tomohiro *et al*., 2004). In the affected joints TNF-α appears as well responsible of the positive regulation and overexpression of chemokines, cytokines and angiogenic molecules which may lead to proliferation and

activation of sinovial cells that, in turn, lead to cartilage and bone destruction (Hata *et al.* 2004). Moreover TNF-α has been implicated in promoting osteoclastogenesis in PsA (Ritchlin *et al.*, 2003). Therapeutic approaches based on anti-TNF-α agents have provided indirect evidence in support to this hypothesis, since they are highly effective in controlling both skin and joint manifestations in patients with PsA (Schopf *et al.*, 2002 & Galadari *et al.*, 2003). Gottlieb (2003), Krueger and Callis (2004) and Mastroianni *et al.* (2005) demonstrated that the marked improvement in both skin and joint manifestations following therapy with Infliximab, a chimeric monoclonal antibody which binds specifically to human TNF-α, was significantly associated to the decrease of serum levels of TNF-α, angiogenic molecules and MMP-2. Some data from large placebocontrolled studies have shown that the medication is highly effective (Gottlieb *et al.*, 2004 & Antoni *et al.,* 2005). Mastroianni *et al.* (2005) described significant decreases of IL-6, VEGF, FGF-b and E-selectin after early infliximab infusions and the significant correlations between PASI and MMP-2, FGF-b or VEGF. Today there are three main biological agents targeting TNF-α, which are already in use for treating PsA. These are the chimeric monoclonal IgG1 antibody infliximab with human constant and murine variable regions, the fully human anti-TNF-α monoclonal antibody adalimumab and the recombinant 75-kDa TNF receptor IgG1 fusion protein etaner-cept (Brandt & Braun, 2006).

Matrix metalloproteinases (MMPs) have been associated with the remodeling of the extracellular matrix during inflammation, neovascularization, and malignant transformation (Suomela *et al.*, 2003). MMPs belong to a family of proteolytic enzymes that are capable of degrading all components of the extracellular matrix, a key event in the development of cartilage destruction and joint erosion (Parks *et al.,* 2004). Kinetic studies using known model substrates have shown that both MMP2 and MMP9 are most effective in degrading collagen as compared to other MMPs (Mackay *et al.*,1990) and have been spec-

ifically implicated in inflammatory arthritis, including angiogenesis (Fraser *et al.*,2001, Alenius *et al.,* 2001& Itoh, *et al.*,2002). MMPs also have a key role in tissue repair (Pilcher *et al.*, 1999). The endothelial activation VEGF and E-selectin molecules are significantly associated to disease activity in psoriasis plaques (Brushan, et al., 1999 & Carducci *et al.,* 1999).

Thiazolidinediones (TZDs) are anti-diabetic agents that enhance insulin sensitivity through activating peroxisome proliferator-activated receptor (PPAR) gamma. Besides their glucose-lowering effects, TZDs are shown to exhibit anti-inflammatory properties in vascular cells, although their precise molecular mechanisms are unknown (Kurebayashi *et al.*, 2005). TZDs have been shown to reduce plasma levels of the chemokine, monocyte chemotactic protein-1 (MCP-1), the anti-fibrinolytic protein, plasminogen activator inhibitor-1 (PAI-1), the endothelial cell adhesion molecules, E-selectin and inter-cellular adhesion molecule-1 (ICAM-1), the leuc-ocyte-activating molecule, CD40L, and the tissue-remodeling enzyme, matrix metall-oproteinase-9 (Buckingham, 2005). Ligand activation of peroxisome proliferator receptor-gamma (a class of nuclear receptors) by thiazolidinediones can normalize the histologic features of psoriasis. So TZDs could be considered as an efficacious and safe agent for the treatment of plaque psoriasis (Shafiq *et al.*, 2005). Our study aimed to investigate the role of MMP-9 in the development of psoriasis by assessing the presence of MMP-9 in lesional skin and in sera of psoriatic patients with & without psoriatic arthritis, the association of MMP-9 with the activity of the disease, the relationship between MMP-9 & TNF-α production as well as to evaluate the effect of pioglitazone (thiazolidinedione) on TNF-α, MMP-9, MMP-2, VEGF and E-selectin production and in treatment of psoriasis.

## Subjects and Methods

### Subjects

Thirty-five psoriatic patients (28 males, 7 females) aged 36–63 years were selected for the present study from

dermatology and rheumatology outpatient clinical at the El- Zahraa and El-Hussein University Hospitals. . They were divided into 2 groups. Group I (PsA) included 15 psoriatic patients (11 males, 4 females) aged 39–63 years, with a clinical diagnosis of psoriatic arthritis (PsA). Group II (Ps) included 20 psoriatic patients without PsA (17males, 3 females), aged 36-62 years. Skin involvement was evaluated with Psoriasis Area and Severity Index (PASI) (Fredriksson & Pettersson, 1978). Arthritis was evaluated following the American College of Rheumatology criteria (ACR) (Mease *et al.,* 2000) with clinical examination of the tender and swollen joints, laboratory tests of inflammatory markers (erythrocyte sedimentation rate = ESR and C-reactive protein = CRP) and radiological examination of joint damage. Each psoriatic patient received pioglitazone 30 mg/day orally for 10 weeks. All participants gave their informed consent before the study began.

**Biochemical analysis**

Venous blood samples (5 ml) were collected after an overnight fasting before and after 10 weeks of pioglitazone treatment. Sera were stored frozen in small aliquots at -80°C, till analysis. Lesional tissue specimens (4 mm punch biopsies) were taken, in the same skin area before and after 10 weeks of pioglitazone treatment. Each tissue sample was rinced in cold sterile medium, weighed after removing fluid excess, and kept in short term culture in a polypropilene tube with 1 ml of complete medium (RPMI 1640 (Sigma,USA), 10% fetal calf serum (FCS), 2 mM L-glutamine, antibiotics) in a 5% $CO_2$ atmosphere at 37°C. After 36 hrs of incubation, the supernatant was collected, spinned in a cold microcentrifuge at 1000 × g and subdivided in small aliquots to be stored frozen at -80°C, till analysis. MMP-9, MMP-2, TNF-α, VEGF& E-selectin concentrations released in culture supernatants from the lesional tissue samples were measured by quantitative enzymelinked immunoassays kit (Quantikine Immunoassays, R&D Systems, Minneapolis,

MN, USA) are based on the double-antibody sandwich method. Results were expressed as pg/ml or ng/ml per milligram of tissue. MMP-9 concentrations were additionally measured in the sera of patients collected concomitantly to skin biopsies.

**Statistical analysis**

Data was entered into IBM compatible computer then analysis were done using SPSS /PC⁺ program for windows (Norusis, 1986). The following statistical procedures were performed (Saunders and Trapp,1990) arithmetic mean, standard deviation (± SD), ″F″ test, one way ANOVA to test for variations within groups (P– values less than 0.05 were considered significant) and correlation coefficient "r" (using spearman's rho) correlation is significant (P <0.01).

## Results

Table 1 & Figures 1 – 5 show that there was a significant increase in TNF-α, MMP-9, MMP-2, VEGF& E-selectin concentrations (P< 0.05) released in culture supernatants from the lesional tissue samples and significant increase in PASI score(P< 0.001) in psoriatic patients with psoriatic arthritis (PsA) as compared to their levels in psoriatic patients without psoriatic arthritis. Table (1) also shows that there was a significant decrease in PASI score & TNF-α, MMP-9, MMP-2, VEGF& E-selectin concentrations in psoriatic patients with and without psoriatic arthritis after 10 weeks of pioglitazone treatment as compared to their levels before pioglitazone treatment.

Table 2 & Figure 6 show that there was a significant increase in serum MMP-9 levels (P< 0.01) in psoriatic patients with psoriatic arthritis (PsA) as compared to their levels in psoriatic patients without psoriatic arthritis. Table 2 also shows that there was a significant decrease in serum MMP-9 in psoriatic patients with and without psoriatic arthritis after 10 weeks of pioglitazone treatment as compared to their levels before pioglitazone treatment.

Table 3 shows significant positive correlations (P< 0.01) between TNF-α & PASI score and MMP-9, MMP-2, VEGF& E-selectin released in tissue culture supernatants from the lesional tissue samples of psoriatic patients without psoriatic arthritis (r=0.9, 0.74, 0.45, 0.59, 0.48 respectively) and after 10 weeks of pioglitazone treatment (r=.0.87, 0.68, 0.53, 0.61, 0.51 respectively).There are also significant positive correlations (P< 0.01) between TNF-α & PASI score and MMP-9, MMP-2, VEGF & E-selectin released in tissue culture supernatants from the lesional tissue samples of patients with PsA (r=0.76, 0.71, 0.52, 0.57, 0.52 respectively) and after 10 weeks of pioglitazone treatment (r=0.85, 0.84, 0.58, 0.63, 0.67 respectively).

Table 4 shows significant positive correlations (P< 0.01) between MMP-9& PASI score and MMP-2, VEGF & E-selectin released in tissue culture supernatants from the lesional tissue samples of psoriatic patients without psoriatic arthritis (r=0.85, 0.43, 0.63, 0.38 respectively) and after 10 weeks of pioglitazone treatment (r=0.95, 0.51, 0.58, 0.45 respectively). There are also significant positive correlations (P< 0.01) between MMP-9& PASI score and MMP-2, VEGF& E-selectin released in tissue culture supernatants from the lesional tissue samples of patients with PsA (r=0.87, 0.45, 0.71, 0.39 respectively) and after 10 weeks of pioglitazone treatment (r=0.82, 0.39, 0.69, 0.41 respectively).

**Table (1): Clinical characteristics and MMP-9, MMP-2, TNF-α, VEGF& E-selectin levels released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after10 weeks of pioglitazone treatment.**

| Parameters | psoriatic patients without PsA before pioglitazone treatment | psoriatic patients without PsA after pioglitazone treatment | PsA patients before pioglitazone treatment | PsA patients after pioglitazone treatment | P < |
|---|---|---|---|---|---|
| Age (years) | 44 ± 12.2 | 44 ± 12.2 | 45 ± 11.5 | 45 ± 11.5 | N.S |
| BMI (kg/m2) | 28.4 ± 5.9 | 28.4 ± 5.9 | 29.6 ± 6.4 | 29.6 ± 6.4 | N.S |
| The duration of Psoriasis (years) | 14.2 ± 8.3 | 14.2 ± 8.3 | 10.7 ± 9.9 | 10.7 ± 9.9 | ------- |
| PASI score | 13.1 ± 7.8 | 6.4 ± 2.9* | 19.4 ± 9.4* | 8.4 ± 5.6* | 0.001 |
| TNF-α (pg/ml) | 216.5 ± 117.4 | 170.9 ± 68.5* | 299.5 ± 125.2* | 197.9 ± 87.8* | 0.05 |
| MMP-9 (ng/ml) | 189.3 ± 170.9 | 46.8 ± 63.7* | 209.6 ± 233.8* | 63.3 ± 84.9* | 0.05 |
| MMP-2 (ng/ml) | 1306 ± 1081 | 1017± 1142* | 1509± 1073* | 1191± 1134* | 0.05 |
| VEGF (pg/ml) | 476.7 ± 298.6 | 230.6 ± 250.1* | 510.9 ± 375.7* | 240.8 ± 270.9* | 0.05 |
| E-selectin (ng/ml) | 12.9 ±17.8 | 5.1 ± 3.8* | 18.7 ± 22.5* | 4.5 ± 3.2* | 0.05 |

Data are expressed as the mean ± SD       Data are normalized per mg of tissue       N.S = non significant
* = Significant (P < 0.05)
- MMP-9, MMP-2, TNF-α, VEGF, E-selectin & PASI score in psoriatic patients without PsA before pioglitazone treatment versus psoriatic patients without PsA after pioglitazone treatment, PsA patients before & after pioglitazone treatment.
- MMP-9, MMP-2, TNF-α, VEGF, E-selectin & PASI score in PsA patients before pioglitazone treatment versus psoriatic patients without PsA before & after pioglitazone treatment and PsA patients after pioglitazone treatment.
- MMP-9, MMP-2, TNF-α, VEGF, E-selectin & PASI score in psoriatic patients with &without PsA after pioglitazone treat-ment versus psoriatic patients with & without PsA before pioglitazone treatment.

**Table (2): Serum MMP-9 in psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**

| Parameters | psoriatic patients without PsA before pioglitazone treatment | psoriatic patients without PsA after pioglitazone treatment | PsA patients before pioglitazone treatment | PsA patients after pioglitazone treatment | P < |
|---|---|---|---|---|---|
| Serum MMP-9 (ng/ml) | 208.7± 45.6 | 106.7 ± 53.7* | 452.4 ± 62.4* | 178.5 ± 44.8* | 0.01 |

Data are expressed as the mean ± SD          * = Significant (P < 0.05)

- Serum MMP-9 in psoriatic patients without PsA before pioglitazone treatment versus psoriatic patients without PsA after pioglitazone treatment, PsA patients before & after pioglitazone treatment
- Serum MMP-9 in PsA patients before pioglitazone treatment versus psoriatic pati-ents without PsA before & after pioglit-azone treatment and PsA patients after pioglitazone treatment.
- Serum MMP-9 in psoriatic patients with &without PsA after pioglitazone trea-tment versus psoriatic patients with & without PsA before pioglitazone treatment.

**Table (3): Correlation between TNF-α & PASI score and MMP-9, MMP-2, VEGF& E-selectin released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**

| Parameters | r psoriatic patients without PsA before pioglitazone treatment | r psoriatic patients without PsA after pioglitazone treatment | r PsA patients before pioglitazone treatment | r PsA patients after pioglitazone treatment |
|---|---|---|---|---|
| TNF-α & PASI score | 0.9* | 0.87* | 0.76* | 0.85* |
| TNF-α & MMP-9 | 0.74* | 0.68* | 0.71* | 0.84* |
| TNF-α & MMP-2 | 0.45* | 0.53* | 0.52* | 0.58* |
| TNF-α & VEGF | 0.59* | 0.61* | 0.57* | 0.63* |
| TNF-α & E-Selectin | 0.48* | 0.51* | 0.52* | 0.67* |

r = correlation coefficient          * = Significant (P< 0.01)

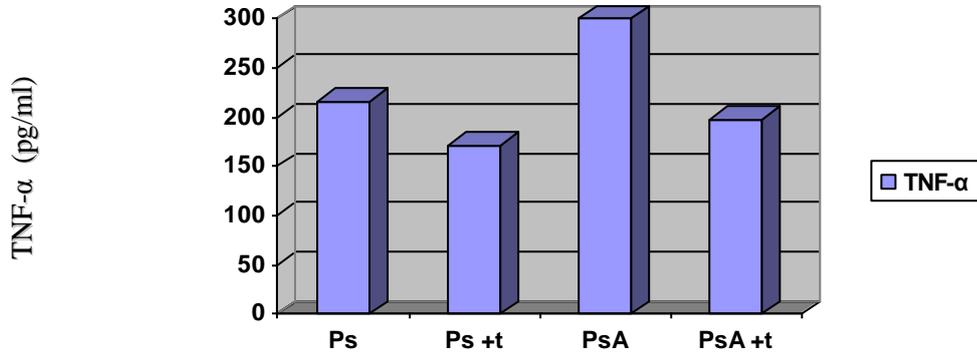**Table (4): Correlation between MMP-9 & PASI score and MMP-2, VEGF& E-selectin released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**

| Parameters | r psoriatic patients without PsA before pioglitazone treatment | r psoriatic patients without PsA after pioglitazone treatment | r PsA patients before pioglitazone treatment | r PsA patients after pioglitazone treatment |
|---|---|---|---|---|
| MMP-9& PASI score | 0.85* | 0.95* | 0.87* | 0.82* |
| MMP-9& MMP-2 | 0.43* | 0.51* | 0.45* | 0.39* |
| MMP-9& VEGF | 0.63* | 0.58* | 0.71* | 0.69* |
| MMP-9& E-Selectin | 0.38* | 0.45* | 0.39* | 0.41* |

r = correlation coefficient          * = Significant (P< 0.01)

**Fig (1): TNF-α levels released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**
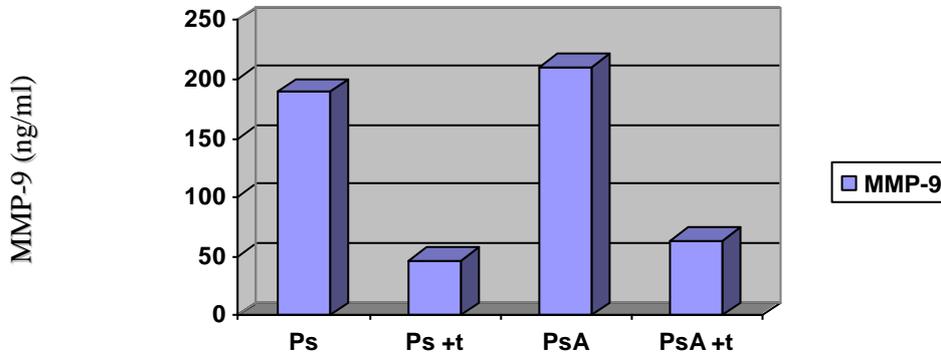


Ps= psoriatic patients without psoriatic arthritis
Ps+ t= psoriatic patients without psoriatic arthritis
after pioglitazone treatment
PsA = psoriatic patients with psoriatic arthritis
PsA+ t = psoriatic patients with psoriatic arthritis
after pioglitazone treatment

**Fig (2): MMP-9 levels released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**
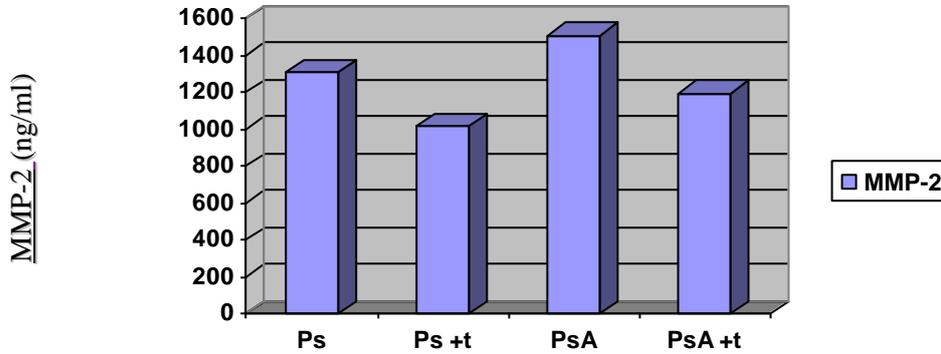
**Fig (3): MMP-2 levels released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**



**Fig (4): VEGF levels released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment.**
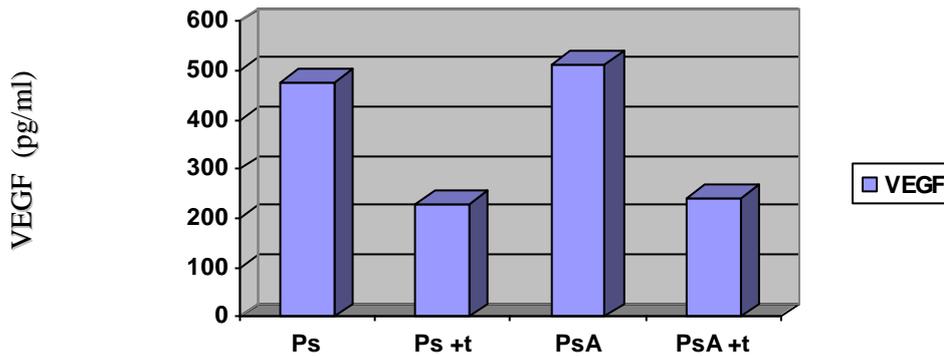


**Fig (5): E-selectin levels released in tissue culture supernatants from the lesional tissue samples of psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment**
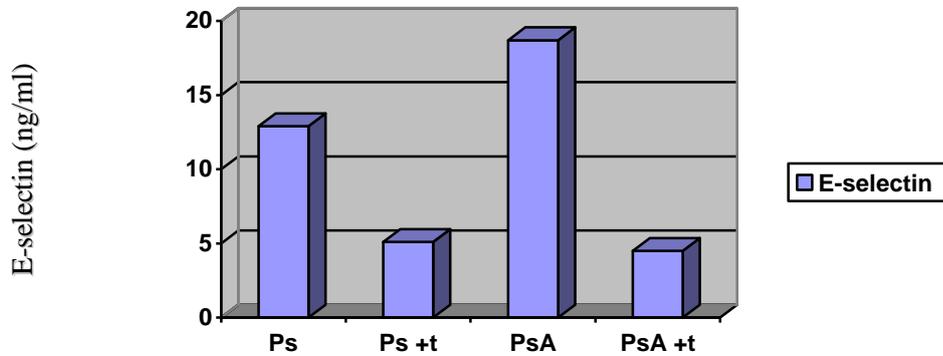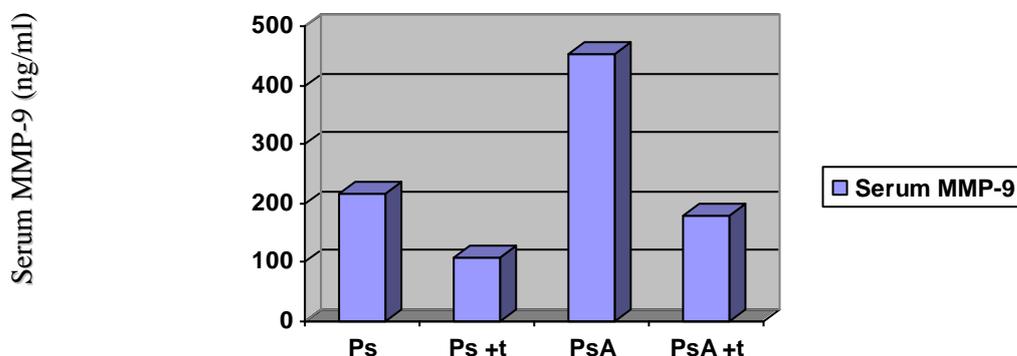
**Fig (6): Serum MMP-9 levels in psoriatic patients with and without psoriatic arthritis before and after 10 weeks of pioglitazone treatment**



## Discussion

Disordered differentiation and hyperproliferation of keratinocytes with inflammation are the hallmarks of psoriasis. Inflammation represents an early and key event in the development of both the cutaneous psoriasis and psoriatic arthritis. Compelling evidences indicate that the production of tumor necrosis factor-α (TNF-α) plays a central role in psoriasis by sustaining the inflammatory process in the skin as well as in the joints. Among the multiple effects produced by TNF-α on keratinocytes, the induction of matrix metalloproteinase-9 (MMP-9), a collagenase implicated in joint inflammatory arthritis which acts as an angiogenesis promoting factor, might represent a key mechanism in the pathogenesis of the disease (Cordiali-Fei *et al.,* 2006). Our results demonstrate that TNF-α, MMP-9, MMP-2, VEGF& E-selectin concentrations released in culture supernatants from the lesional tissue samples and serum MMP-9 levels in psoriatic patients with psoriatic arthritis (PsA) were significantly elevated as compared with psoriatic patients without psoriatic arthritis. TNF-α is considered a key cytokine regulator in psoriasis (Victor *et al*., 2003). As expected, the lesional amounts of TNF-α were directly correlated with the PASI score, sustaining its pathogenic role in the development of skin psoriasis. The correlation found between MMP-9 and PASI, suggests that also this molecule may be involved in the inflammatory process leading to the cutaneous lesions. Indeed, TNF-α act as a potent inducer of MMP-9 in keratinocytes (Tomohiro *et al*., 2004). Therefore, TNF-α mediated induction of MMP-9 could be responsible of the overexpression and activity of this molecule as found in the synovial cells and skin of patients with PsA (Hitchon et al., 2002, Giannelli et al., 2004 & Kane *et al*., 2004). On the other hand, MMP-9 can be also secreted by inflammatory cells, such as neutrophils, upon activation by the IL-8 family proteins (Chakrabarti & Patel, 2005). Moreover, MMP-9 mediates terminal cleavage of IL-8, thus potentiating IL-8-induced activation of neutrophils. This suggests that MMP-9 can be involved as a mediator of the IL-8-induced inflammatory process in the psoriatic skin (Van de Steen *et al*., 2000). Other data obtained by immunohistochemical analysis of psoriatic skin and synovia in individuals under infliximab treatment showed that the drug decreased the neoangiogenesis and reduced the activation of the endothelial cells resulting in decreased cell infiltration and clinical improvement (Goedkoop *et al*., 2004).

Thiazolidinediones (TZDs) are important new drugs, presently indicated for the treatment of type 2 diabetes but with a spectrum of properties which suggests their potential for treating a number of degenerative inflammatory diseases. At the

tissue level, TZDs improve vascular endothelial function, and reduce the rate of progression of intimal-medial thickening of the carotid artery and the microalbuminuria of type 2 diabetes. Further, TZDs have been shown to be efficacious in inflammatory diseases as wide-ranging as psoriasis, ulcerative colitis and non-alcoholic steatohepatitis (Buckingham, 2005). Bhagavathula *et al*. (2004) observed that pioglitazone and rosiglitazone (potent TZDs) inhibited proliferation and motility as well as elaboration of MMP-1 and MMP-9. Inhibition was obtained with keratinocytes in monolayer culture and human skin in organ culture. Because enhanced keratinocyte motility and increased MMP production as well as increased keratinocyte proliferation are thought to contribute to the phenotype of psoriatic lesional skin, they propose that interference with these keratinocyte responses contributes to the previously reported antipsoriatic activity of TZD. In the present study we found that the clinical improvement of the skin expression of the disease in patients with and without psoriatic arthritis under pioglitazone therapy significantly correlated with the decrease of lesional MMP-9 in association with the decrease of TNF-α, or VEGF and E-selectin, bioactive molecules already known to be implicated in the pathogenesis and clinical activity of the disease (Bonifati & Ameglio 1999). Activation of peroxisome proliferator activated receptor gamma (PPAR gamma) by rosiglitazone or pioglitazone significantly reduced TNF-alpha and PMA induced MMP-9 gelatinolytic activity, but did not alter the expression of tissue inhibitor of MMPs type 1 (TIMP-1), the local inhibitor of MMP-9 (Hetzel *et al*., 2003). Liu *et al*. (2003) observed that treatment of the highly aggressive human breast cancer cell line MDA-MB-231 with the synthetic PPARgamma ligands pioglitazone or rosiglitazone, at concentrations at

which no obvious cytotoxicity was observed in vitro, led to a significant inhibition of MMP-9 activities. They suggest that PPARgamma ligands may have therapeutic value for the treatment of highly invasive breast cancer by targeting its invasive behavior.

## Conclusion

The current study shows the existence of a direct relationship between MMP-9 and TNF-α production strongly suggesting that MMP-9 may play a key role in the skin inflammatory process. Our findings also demonstrating that pioglitazone could be considered as an efficacious and safe agent for the treatment of psoriasis. The optimum dose and duration of pioglitazone therapy remain to be determined.

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# تأثير البيوجليتازون على الماتركس متالوبروتينيز -9 و الماتركس متالوبروتينيز -2 والتنكرز الورمى الفا وعامل النمو للغشاء المبطن للوعاء الدموى و السليكتين فى الاصابة الجلدية المصاحبة لمرض الصدفية فى وجود وعدم وجود التهاب المفاصل

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**المقدمة :** من اكثر الامراض الجلدية شيوعا الصدفية و قد يصاحبها توغل الخلايا التى تسبب الالتهابات فى الطبقة العميقة من الجلد مما يسبب تهيج خلايا الكرياتين . والهدف من هذا البحث دراسة الدور الذى يلعبه الماتركس متالوبروتينيز-9 فى الاصابة بالصدفية بواسطة قياس وجوده فى الاصابة الجلدية وفى مصل الدم لمرضى المصابين بالصدفية فى وجود وعدم وجود التهاب المفاصل ومعرفة العلاقة بين التنكرز الورمى الفا و الماتركس متالوبروتينيز-9 ونشاط المرض وهذا بالاضافة الى معرفة كفائة البيوجليتازون فى علاج الصدفية .

**المرضى وطرق البحث :** اجرى هذا البحث على 35 مريضا بالصدفية وقد قسموا الى مجموعتين , المجموعة الاولى تضم 15 مريضا مصابون بالتهاب المفاصل مع الاصابة الجلدية , والمجموعة الثانية تضم 20 مريضا مصابون بالاصابات الجلدية ولا يعانون من اى التهاب مفصلى . كل مريض بالصدفية اخذ علاج 30مجم من البيوجليتازون يوميا عن طريق الفم لمدة 10 اسابيع . وقد تم اخذ عينة من الجلد المصاب وكذلك عينة من الدم قبل وبعد العلاج من كل مريض فى هذا البحث . وتم قياس الماتركس متالوبروتينيز -9 و الماتركس متالوبروتينيز -2 والتنكرز الورمى الفا وعامل النمو للغشاء المبطن للوعاء الدموى و السليكتين بواسطة الاليزا فى السائل الطافى من الوسط المستخدم فى زرع الانسجة الجلدية المصابة وتم قياس الماتركس متالوبروتينيز -9 فى مصل الدم ايضا بواسطة الاليزا .

**النتائج :** وقد اوضحت النتائج والكشف الطبى ان جميع المرضى قد تحسنوا تحسنا واضحا بعد عشر اسابيع من العلاج بالبيوجليتازون وهذا التحسن يصاحبه نقص ذو دلالة احصائية فى مستوى الماتركس متالوبروتينيز -9 و الماتركس متالوبروتينيز -2 والتنكرز الورمى الفا وعامل النمو للغشاء المبطن للوعاء الدموى و السليكتين .

وقد وجد ارتباطا ذو دلالة احصائية بين الماتركس متالوبروتينيز -9 والتنكرز الورمى الفا ونشاط المرض .

**الخلاصة :** قد اكدت النتائج ارتباطا ذو دلالة احصائية بين الماتركس متالوبروتينيز -9 والتنكرز الورمى الفا ونشاط المرض وهذا يؤكد ان الماتركس متالوبروتينيز -9 له دور مهم فى الالتهابات الجلدية المصاحبة لمرض الصدفية . وقد اكدت الدراسة ايضا ان العلاج بالبيوجليتازون له تاثير فعال فى علاج الصدفية ولذا يمكن أن ننصح باستعماله كعلاج ناجح وفعال و آمن فى علاج الصدفية ولكن نحتاج لمزيد من الابحاث لتحديد الجرعة الفعالة ومدة العلاج اللازمة لعلاج الصدفية .