Correlation of MRP8/MRP14 and S100A12 with disease activity in rheumatoid and psoriatic arthritis

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Abstract: *Objective:* To evaluate myeloid-related protein MRP8/MRP14 (S100 protein) and S100A12 in the serum and synovial fluid of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients and its relation to local and systemic parameters of disease activity. *Methodology:* Thirty RA patients (Group I), twenty five PsA patients (Group II) and ten controls (Group III) were included in the study. The patients were subjected to through history taking and clinical examination. Synovial fluid (SF) aspiration was done from twenty RA patients and ten PsA patients. ESR, CRP and synovial fluid analysis for white blood cell count, lymphocytes%, and acute phase serum amyloid (A-SAA) were performed. MRP8/MRP14 and S100A12 were assessed with ELISA technique in serum and synovial fluid samples. *Results:* Serum level of MRP8/MRP14 and S100A12 were elevated in Groups I and II in comparison to group III. The serum and synovial levels of MRP8/MRP14 and S100A12 in Group I and II showed no significant difference. The MRP8/MRP14 and S100A12 in group I showed significant positive correlation with disease activity score (DAS), ESR, CRP, SF MRP8/MRP14, SF S100A12, SF WBCs, lymphocytes% and A-SAA. The SF MRP8/MRP14 and SF S100A12 in group I showed positive significant correlation with ESR, DAS, SF-WBCs, lymphocytes and A-SAA. Group II showed a positive significant correlation of MRP8/MRP14 and S100A12 with ESR, CRP, DAS and psoriasis area and severity index (PASI). The SF- MRP8/MRP14 and SF S100A12 in group II showed a positive significant correlation with local inflammatory markers. *Conclusions:* The elevated MRP8/MRP14 and S100A12 in the serum and synovial fluids of patients with RA and PsA showed a significant correlation with local and systemic disease activity parameters. So, it can be used to monitor disease activity and patient's response to treatment.
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Key Words: Rheumatoid arthritis (RA), Psoriatic arthritis (PsA), Myeloid- related protein (MRP8/MRP14), S100A12.

Introduction:

S100 proteins are calcium-activated signaling proteins that interact with target proteins to modulate biological process (Broome et al., 2003). The myeloid related protein 8 [MRP-8(S100A8)] and 14 [MRP-14(S100A9)] are 2 calcium – binding S100 proteins expressed and released by phagocytes, which are markers for interactions between endothelial cells and macrophages in inflammatory arthritis. Both proteins are specially secreted by phagocytes at local sites of inflammation (Frosch et al., 2000). By interacting with specific binding sites on endothelial cells, extracellular complexes of MRP-8 and MRP-14 promote adhesion of phagocytes. In parallel MRP-8/MRP-14 activate the integrin receptor CD 11b/CD18 on phagocyte and modulate migration of leucocytes (Mantiz et al., 2003 and Roth et al., 2003).

MRP8 and MRP14 are secreted by monocytes during an interaction with inflammatory activated endothelial cells (Rammes et al., 1997), and complexes of both proteins exhibit direct pro-inflammatory effects (Donato 1999). MRP8/MRP14 heterodimers mediate the adherence of leucocytes to endothelial cells and promote subsequent trans-migration (Srikrishna et al., 2001). The extracellular MRP14 induces the up regulation of CD11b/CD18 integrin binding activity on neutrophils and monocytes (Eue et al., 2000 and Newton & Hogg 1998).

S100 proteins play a role in both intracellular functions, such as cell differentiation and cell cycle progression, regulation of kinase activities and cytoskeleton –membrane interactions, and extracellular functions such as inducing neutrophil extension, chemo-attraction, and the induction of adhesion molecule expression (Donato 1999) .

MRP8 and MRP14 are expressed in high concentrations in infiltrating granulocytes and monocytes and during the stages of early differentiation of monocytes, but are absent in lymphocytes and mature tissue macrophages (Kerkhoff

et al., 1998). The expression of MRP8/MRP14 in inflammatory synovitis points to a positive feedback mechanism by which the contact of phagocytes with activated endothelium leads to the release of MRP8/MRP14, which induces firm adhesion and transmigration of infiltrating cells to the synovial tissue (Kane et al., 2003).

S100A12 (EN-RAGE) is secreted by activated granulocytes and binds to the receptor for advanced glycation end products , which induces nuclear factor (NF) -kB- dependent activation of endothelium (Foell et al; 2003). Increased serum levels of S100A12, a proinflammatory protein secreted by activated neutrophils, have recently been shown in patients with active inflammatory diseases, such as RA and Kawasaki disease (Komatsuda et al; 2006). S100A12 is associated with coronary atherosclerosis plaque rupture as it is expressed in vascular smooth muscle accelerating atherosclerosis and plaque instability (Hofmann Bowman et al; 2011). Also it is extensively expressed at local sites of inflammation in cystic fibrosis (Foell et al; 2003) .

Myelomonocytic cells play a key role in the production and perpetuation of synovial inflammation in seropositive and seronegative inflammatory arthritis. The synovitis of rheumatoid arthritis is characterized by infiltration of macrophages and, to a lesser extent, neutrophils which contribute directly to joint inflammation and destruction through the production of proinflammatory cytokines and proteolytic enzymes, such as metalloproteinase (Burmester et al., 1997). Macrophage infiltration and metallo-proteinase production in the synovium correlates with the development of joint erosion (Cunnane 2001) and specific therapies targeted at macrophage products such as tumor necrosis factor (TNF) with anti-tumor necrosis factor (anti-TNF) (Van den Bosch et al., 2000) .

However, Psoriatic arthritis is characterized by less joint destruction than RA (Goldman et al., 1990) and Psoriatic arthritis synovium has been reported to have fewer infiltrating macrophages (Veale et al., 1993) and reducing TNFα production (Danning et al., 2000). This may be due to a reduction in myelomonocytic cell trafficking and activation in the synovium. Broome et al. (2003) studied the level of expression and cellular localization of S100A7, S100A8, S100A9, S100A10 and S100A11 in normal and psoriatic epidermis. They found that S100A7 and S100A11 were present in the basal and spinous layers in normal epidermis. These proteins appear in the nucleus and cytoplasm in basal cells but are associated with the plasma membrane in spinous cells. S100A8 and S100A9 are absent or are expressed at minimal levels in normal epidermis .

In involved psoriatic tissue, S100 A10 and S100A 11 levels remain unchanged, whereas, S100 A7, S100A8, and S100A9 are markedly over expressed. The pattern of expression and subcellular localization of S100A7 is similar in normal and psoriatic tissue. S100A8 and S100A9 are strongly expressed in the basal and spinous layers in psoriasis-involved tissue. They concluded that S100A7, S100A8 and S100A9 expression is markedly altered in psoriasis, suggesting a role for these proteins in disease pathogenesis .

Aim of the work:
The aim of our work was to evaluate the myeloid related protein MRP8/MRP14 and S100A12 in the serum and synovial fluid of RA and PsA patients and to evaluate their correlation with local and systemic parameters of disease activity.

Subjects and methods:
Thirty RA patients (Group I), 25 PsA patients (Group II) and 10 normal healthy subjects as a control group (Group III) were included in the study. They were recruited from Ain Shams University Hospitals over 6 months. RA patients met the American Colleague of Rheumatology (ACR) 1987 revised criteria for the diagnosis of RA (Arnett et al., 1988). PsA patients were diagnosed according to the Classification Criteria for Psoriatic Arthritis (CASPAR) (Taylort et al., 2006). This consists of established inflammatory articular disease with at least 3 points from the following features: current psoriasis (assigned a score of 2; all other features were assigned a score of 1), a history of psoriasis (unless current psoriasis was present), a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis), dactylitis, juxta-articular new bone formation, rheumatoid factor negativity and nail dystrophy .
All patients were subjected to:
Full history taking:
Duration of illness, morning stiffness, medical treatment received and its duration.
Thorough clinical examination:
Included general and musculo-skeletal examination of axial and peripheral joints with special emphasis on:
 -Ritchie articular index (Ritchie et al., 1968); number of tender joints (28 joints were examined including both shoulders, both elbows, both wrists, both knees, bilateral all metacarpophalangeal and all proximal interphalangeal joints.
  -Swollen joint count: the same 28 joints as tender joints were examined.
   -Patient's global assessment of disease activity measured by visual analogue pain scale (VAS) of 100 mm (Prevoo et al., 1995).

-Disease activity score (DAS 28) which measures disease activity (Van der Heijde et al., 1990). The activity was calculated as follow: DAS28 (4) = $(0.56*sqrt (t28) + 0.28*sqrt (sw28) + 0.70*Ln (ESR) + 0.014*GH$

t28 = number of painful joints from 28 joints
sw28 = number of swollen joints from 28 joints
ESR = erythrocyte sedimentation rate in mm/first hour
GH = general health by assessment on 0 to 100 mm VAS.

High disease activity >5.1, moderate > 3.2 and < or = 5.1), low disease activity <3.2, remission <2.6 (Pincus et al., 2000).

-Psoriasis severity: this done by using psoriasis area and severity index score (PSAI) (Fredrikssen and Patterson 1978). The body surface area is classified into:

Head (H) which represent 10% of the total body surface area; Trunk (T) 30%, Upper extremity (U) 20%, Lower extremity (L) 40%.

The extent of area involved (A) is graded according to the following scale:
0=none   1=<10%   2=>10%-30%   3=>30%-50% 4=>50%-70% 5=>70%-90% 6=>90%-100%

Each area involved was checked for Erythema (E), Induration (I) and Desquamation (D), and given subjectively the score from 0-4 according to:
None (0), Mild (1), Moderate (2), Severe (3) and Very Severe (4).

The PSAI is then calculated with the following formula:
PASI= [(EH + IH + DH) x AH] x 0.1+ [(ET +IT + DT) x AT] x 0.3 + [(EU + IU + DU)] x AU] x 0.2 + [(EL + IL + DL)] x AL] x 0.4

The severity is considered mild if PASI value is less than 15, moderate if it is between 15-25 and severe if it is more than 25.

Laboratory investigations:
Sampling:
1- Peripheral venous blood samples were obtained from all patients and controls. One ml of blood added to tube containing sodium citrate for ESR measurement. The remaining blood sample was left for coagulation for 30 minutes, then centrifuged at 1000 Xg for 20 minutes to separate serum that, was aliquoted , labeled and stored at -80◦C until performing the MRP8/ MRP14 and S100A12 .

2- Synovial fluid aspiration from the suprapatellar pouch of the knee joint under complete aseptic condition from 20 RA patients and 10 PsA patients. The SF sample was tested for white blood cell count/ mm² (SF WBCs and lymphocytes %). The rest of it was treated by protease inhibitor (Roche Diagnostic, Meylan, France) and centrifuged at 1000 Xg for 20 minutes. The supernatant fluids were stored at -80◦C to

be used for assessment of MRP8 / MRP14 and S100A12 as well as synovial fluid acute phase serum myeloid A (SF A –SAA). Immediately before analysis, the synovial fluid were thawed and pretreated for 1 hour with hyaluronidase (Sigma, St. Louis, MO), and centrifuged for 10 minutes at 1000 Xg and the supernatant was collected.

Methods of laboratory investigations:
1-Erythrocyte sedimentation rate mm/hour (ESR) measured with Westergren method with vaccum blood collection tube.
2-C-reactive protein (CRP) measured with immunoturbidimetric method.
3-Intraarticular markers of inflammation were assessed by measuring synovial white blood cell count/ mm³ (SF WBCs and lymphocytes %) by diluting SF sample with isotonic 0.1% toluidine blue , then counting using Fuchs-Rosenthal ruled counting chamber. WBCs differentiated by examining leishman stained smear of sediment from centrifuged SF. Also, Synovial fluid acute phase serum amyloid A (SF A–SAA) was measured with an enzyme linked immunosorbent assay kit (Life Diagnostics Inc., West Chester, USA).
4-Assessment of S100A12: Determination of serum and SF S100A12 were performed by enzyme linked immunosorbent assay (ELISA), using commercially available ELISA kit, provided from Uscn, Life Diagnostics Inc., USA, according to the manufacture instruction. Biotin-conjugated polyclonal antibody preparation specific for S100A12 was used. The assay has a sensitivity of 5.9 pg/ml.
5-Assessment of MRP8 / MRP14: Enzyme-linked immunosorbent assay (ELISA): Rabbit antisera against MRP8 and MRP14 were used for serum and SF then, the monospecificity of the antibodies analyzed by immunoreactivity against recombinant MRP8 and MRP14 , by Western blot analysis of lysates of monocytes and granulocytes, as well as immunoreactivity against MRP8 and MRP14 transfected fibroblastic cell lines. Different amount of MRP8 and MRP14 (0.25-250 ng/ml) were used for calibration. The assay has a sensitivity of 0.5 ng/ml and a linear range between 1- 30 ng/ml. MRP8 and MRP14 form non-covalent associated complexes in the presence of extracellular calcium concentrations that are detectable by ELISA system. The ELISA then calibrated with the native MRP8 / MRP14 complex, and the data was expressed as ng/ml of MRP8 /MRP14.

Statistical analysis
It was performed using statistical software package (SPSS) version 15. Descriptive data of patients were expressed as mean ± SD. Student's t test was used to compare between two independent samples. While,

Pearson correlation coefficient analysis used in assessing the strength of association between two variables. P values less than 0.05 were considered significant. Also, Wilcoxon Rank Sum Test is used to compare non parametric variables.

Results:

This study was conducted on 30 patients (20 females and 10 males) with RA (Group I), their age ranged from 39 to 60 years with a mean age (48.56±5.16 years). There were 20 patients with knee effusion and the patients were receiving non-steroidal anti-inflammatory drugs (NSAIDS), cortisone and disease modifying drugs mainly methotrexate and hydroxyl-chloroquine in different combinations. Their descriptive data are shown in table (1).

The psoriatic arthritis patients (Group II) were 25 (15 females and10 males), their age ranged from 39 to 60 with a mean (47.84± 5.26 years). There were 10 patients with knee effusion, the patients were receiving, PUVA, methotrexate and or NSAIDS. Descriptive data of psoriatic arthritis (PsA) are shown in table (2) .

On comparing the patients and control groups as regard age; there was no significant difference between RA patients (Group I) and control (Group III) as well as between PsA (Group II) and control. There was a highly significant increase in the MRP8/MRP14 and S100A12 levels in RA and PsA in comparison to the control group (Table 3).

On comparing Group I and Group II, the Results showed no statistical significant difference between them as regard: age, duration of disease, level of MRP8/MRP14 and S100A12 in the serum or in synovial fluid, inflammatory markers in synovial fluids as white blood cell count, lymphocytes and acute phase amyloid A. There were a highly significant difference in the activity parameters as morning stiffness, DAS, RAI, swollen joint count, ESR, CRP between group I (RA) and group II (PsA) (Table 4).

Table (1): Descriptive data of group I (RA)

Parameter	Range	Mean±SD
Age (years)	39-60	48.56±5.16
Duration (months)	10-40	21.1±8.6
Morning stiffness (min)	10-90	40.5±19.8
RAI	6-26	13.86±4.84
Swollen joint count	8-22	14.33±3.48
ESR (mm/h)	38-100	63.26±18.69
CRP (mg/l)	40-90	59.06±15.73

DAS	3.1-7.2	5.2±1.37
MRP8/MRP14 (ng/ml)	11-17.41	14.79±2.04
S100A12 (pg/ml)	49-350	183±85.3
SF MRP8/MRP14 (ng/ml)	12.24-18.49	15.66±1.91
SF S100A12 (pg/ml)	325-1000	684±227
SF WBCs (mm³)	1300-2300	1705±348.6
SF Lymphocytes (mm³)	60-150	103.25±24.88
A-SAA (ug/ml)	49-98	70.85±15.17

Data: Range and Mean ± SD

Table (2): Descriptive data of group II (PsA)

Parameter	Range	Mean±SD
Age (years)	39-60	47.84±5.26
Duration (months)	10-60	25.44±12.90
Morning stiffness (min)	5-30	16.6±7.73
RAI	2-18	5.68±3.72
Swollen joint count	1-16	4.92±3.43
ESR (mm/h)	10-60	34.44±12.00
CRP (mg/l)	10-50	29.6±10.98
DAS	2.4-6	4.01±0.99
PASI	8-30	19.96±6.58
MRP8/MRP14 (ng/ml)	12.17-17.98	15.59 ±1.51
S100A12 (pg/ml)	49-250	155±57.7
SF MRP8/MRP14 (ng/ml)	13.34-18.1	15.87±1.81
SF S100A12 (pg/ml)	195-921	526±217
SF WBCs (mm³)	1500-2300	1836±263.10
SF Lymphocytes (mm³)	80-150	111.5±26.14
A-SAA (ug/ml)	50-86	67±11.29

Data: Range and Mean ± SD

*Table (3): Comparison of patients (group I and II) and control groups*

|		Mean±SD	Group III(Control)	t	p	Sig
Group I (30 RA)	Age MRP8/MRP14(ng/ml) S100A12 (pg/ml)	48.56±5.16 14.79±2.04 183±85.3	48±6.7 1.46±0.30 47±17.2	-0.243 -34.544 4.95	>0.05 <0.001 <0.0001	NS HS HS
Group II (25 PsA)	Age MRP8/MRP14(ng/ml) S100A12 (pg/ml)	47.84±5.26 15.59±1.51 155±57.7	48±6.7 1.46±0.30 47±17.2	0.067 -44.338 5.78	>0.05 <0.001 <0.0001	NS HS HS

NS=non-significant.   HS=highly significant.

Table (4): Comparison between group I (RA) and group II (PsA)

|	GI (RA)	GII (PsA)	t	Z	p	Sig
Age (years)	48.56± 5.16	47.84± 5.26	0.514		>0.05	NS
DAS	5.2± 1.37	4.01± 0.99	3.700		<0.001	HS
MRP8/MRP14 (ng/ml)	14.79±2.04	15.59±1.51	-1.662		>0.05	NS
S100A12 (pg/ml)	183±85.3	155±57.7	1.36		>0.05	NS
SF MRP8/MRP14 (ng/ml)	15.66±1.91	15.87±1.81	-0.294		>0.05	NS
SF S100A12 (pg/ml)	684±227	526±217	1.82		>0.05	NS
SF WBCs (mm³)	1705±348.6	1836±263.10	-1.148		>0.05	NS
SF Lymphocytes (mm³)	103.2±24.88	111.5±26.14	-0.827		>0.05	NS
A-SAA (ug/ml)	70.85±15.17	67±11.29	0.781		>0.05	NS
Duration (months)	21.1±8.6	25.44±12.90		-1.126	>0.05	NS
Morning stiffness	40.5±19.8	16.6±7.73		-5.115	<0.001	HS
RAI	13.86±4.84	5.68±3.72		-5.340	<0.001	HS
Swollen joint count	14.33±3.48	4.92±3.43		-5.844	<0.001	HS
ESR (mm/h)	63.26±18.69	34.44±12.00		-5.340	<0.001	HS
CRP (mg/l)	59.06±15.73	29.6±10.98		-5.752	<0.001	HS
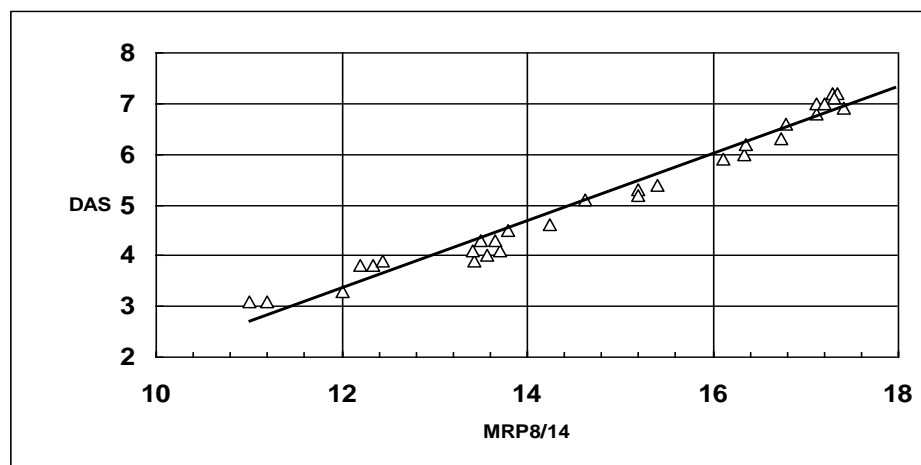
Figure (1): Regression analysis showing the correlation between MRP8/MRP14 and DAS among RA patients
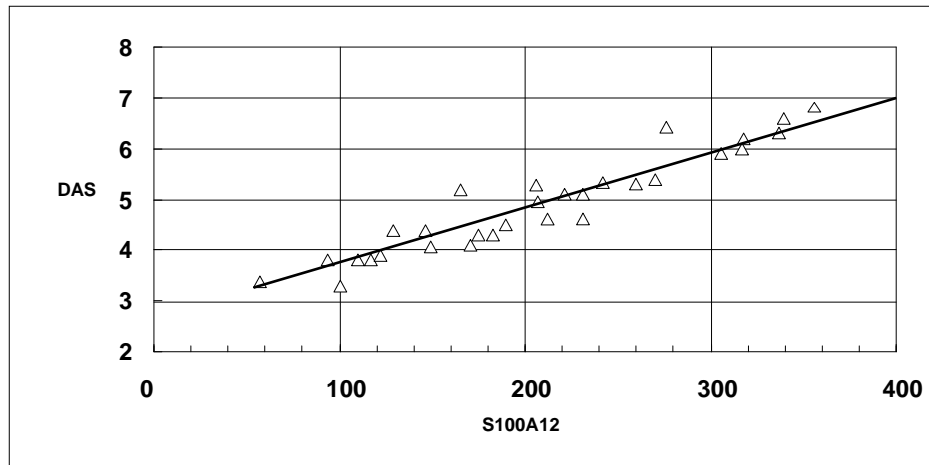
Figure (2): Regression analysis showing the correlation between S100A12 and DAS among RA patients
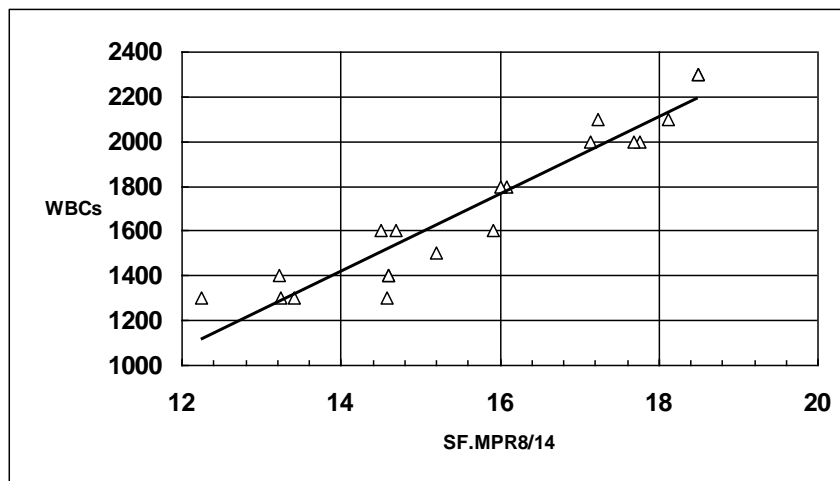
Figure (3): Regression analysis showing the correlation between SF MRP8/MRP14 and WBCs among RA patients
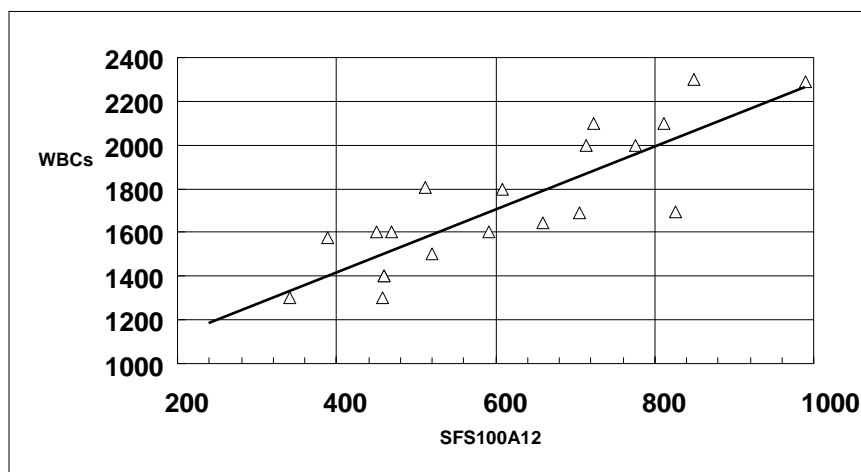
Figure (4): Regression analysis showing the correlation between SF S100A12 and WBCs among RA patients

The results showed a positive significant correlation of MRP8/MRP14 and S100A12 levels in the serum of Group I (RA) with ESR (r=0.84 & 0.81), CRP (r=0.70 & 0.82) and DAS (r=0.98 & 0.74) respectively with p<0.05 (Figure 1&2). Also there was a positive significant correlation of serum level of MRP8/MRP14 and S100A12 with SF level of MRP8/MRP14 and S100A12 (r =0.98 & 0.92), SF WBCs (r = 0.93 & 0.70), Lymphocytes (r=0.98 & 0.78) and acute phase serum amyloid A (r= 0.99 & 0.68).

The results showed a positive non significant correlation between serum level of MRP8/MRP14 and S100A12 of RA group with morning stiffness (r=0.20 & 0.14), Ritchie articular index (r=0.33 & 0.25) and swollen joint count (r=0.07 & 0.18).

The results showed a positive significant correlation of SF MRP8/MRP14 and SF S100A12 in Group I with ESR (R= 0.81 & 0.64), CRP (R= 0.57 & 0.81), DAS (r=0.97 & 0.61) and with local activity parameters as SF WBCs (r=0.93 & 0.51) (Figure 3&4), Lymphocytes (r=0.98 & 0.68) and ASAA (r= 0.98 & 0.97).

The synovial fluid level of MRP8/MRP14 and S100A12 in RA patients showed negative non significant correlation with morning stiffness (-0.01 &

-0.13) and swollen joint count (r=-0.07 & -0.17) and positive non significant correlation with Ritchie articular index (r= 0.27 & 0.09).

The results of Group II (PsA) showed that, serum levels of MRP8/MRP14 and S100A12 had a positive significant correlation with ESR (r=0.85 & 0.57), CRP (r=0.60 & 0.52), DAS (r=0.99 & 0.78) and PASI (r=0.53 & 0.68) (Figure 5&6).While, it had a non-significant negative correlation with morning stiffness (r=-0.12 & -0.09), RAI (r=-0.12 & -0.11) and swollen joint count (r=0.09 & -0.17).

The SF MRP8/MRP14 and SF S100A12 in group II (PsA) showed a significant positive correlation with local inflammatory parameters in the synovial fluid as WBCs (r=0.98 & 0.96), lymphocytes (r=0.95 & 0.89) and A SAA (r=0.98 & 0.98) (Figure 7&8).

Also, PsA patients results showed a non significant positive correlation of SF MRP8/MRP12 and SF S100A12 with morning stiffness (r=0.11 & 0.07), ESR (r=0.17 & 0.09), CRP (r=0.32 & 0.18) and PASI (r=0.21 & 0.7). The non significant negative correlation was with RAI (r=-0.35 & -0.23), swollen joint count (r=-0.35 & -0.19), DAS (-0.02 & -0.07) and MRP8/MRP14 (r= -0.02 & -0.11).
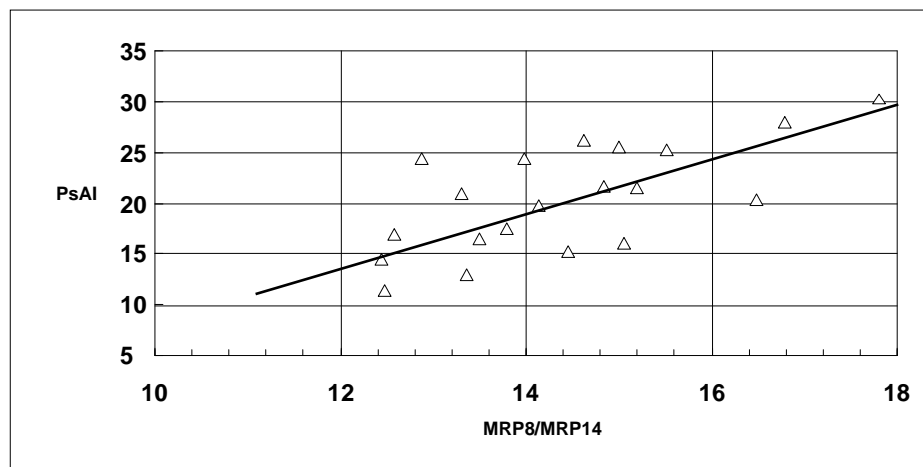
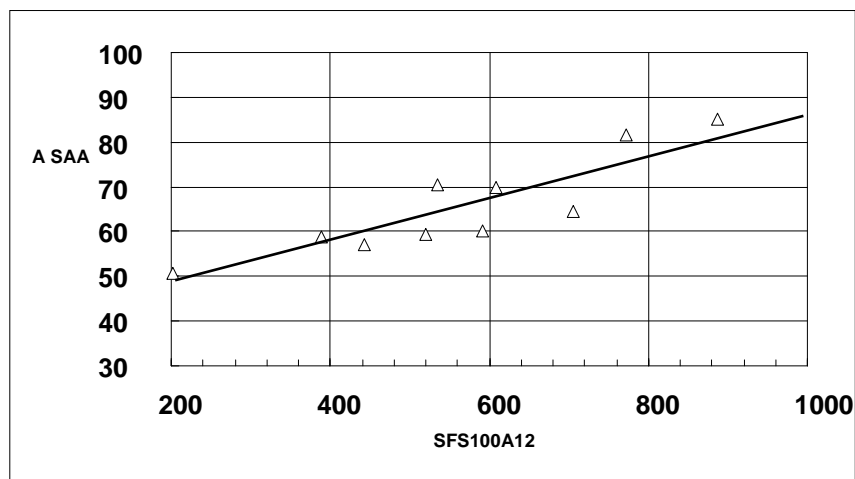*Figure (5): Regression analysis showing the correlation between MPR8/14 and PsAI among PsA patients*
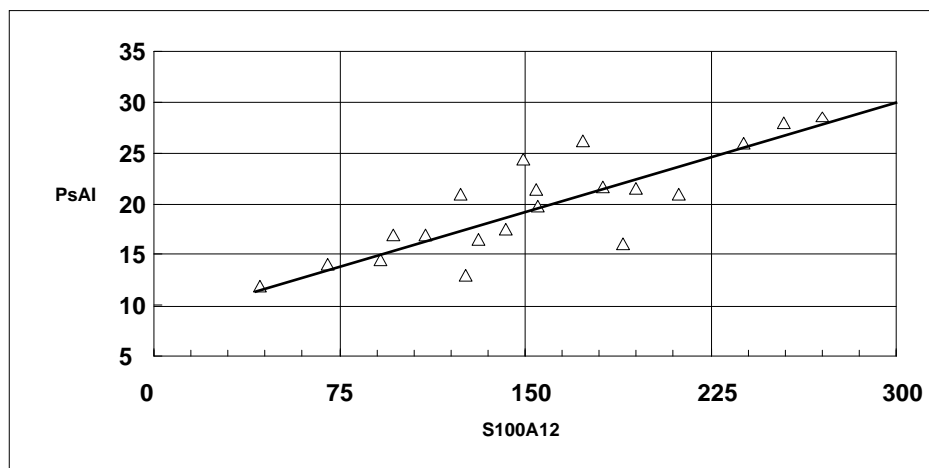
Figure (6): Regression analysis showing the correlation between S100A12 and PsAI among PsA patients
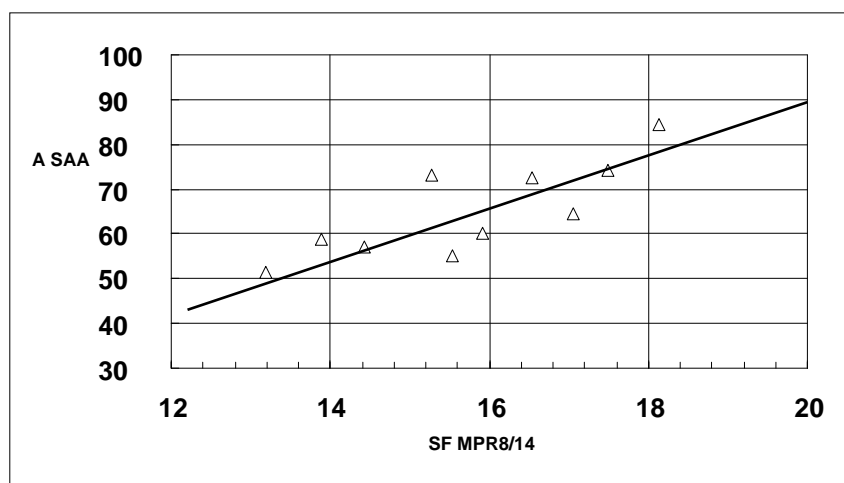
Figure (7): Regression analysis showing the correlation between SF MPR8/14 and A-SAA among PsA patients

Figure (8): Regression analysis showing the correlation between SF S100A12 and A-SAA among PsA patients

Discussion:

The myeloid related protein 14 (MRP14), also known as S100 A9, calgranulin B (Healy et al., 2006), is a member of a family of proteins that have intracellular and extracellular roles modulating calcium signaling, arachidonic acid metabolism, cytoskeletal reorganization and trafficking of neutrophils (Donato, 2003).

In humans, the most abundant form of MRP-14 is MRP-8/14, in which MRP-14 is bound to MRP-8 (Nacken et al., 2003). Although, MRP-8/14 is highly expressed in neutrophils, some authors found that platelets and megakaryocytes also contain MRP-14 mRNA and that; platelets express MRP-8/14 protein (David et al., 2008).

S100A12 (calgranulin C; extracellular newly identified RAGE binding protein, EN-RAGE) is more restricted to granulocytes (Vogal et al., 1999). S100A8, S100A9 and S100A12 are found in high concentrations in inflamed tissue, where neutrophils and monocytes belong to the most abundant cell types. They exhibit proinflammatory effects in vitro at concentrations found at sites of inflammation in vivo. Although, S100A12 binds to RAGE, at least part of the proinflammatory effects of the S100A8/S100A9 complex depend upon interaction with other receptors (Foell et al., 2007).

The results of this study, showed non-significant difference between patients and controls as regard age. However, there was a highly significant increase in the MRP8/MRP14 and S100A12 in patients groups in comparison to the control. The increase of MRP8/MRP14 and S100A12 were 10 fold higher in patients than the control. These results were similar to

the results of Frosch et al. (2003) where they found that the serum concentrations of MRP8/MRP14 were 120 fold higher in systemic onset Juvenile RA compared with healthy controls and approximately 12 fold higher when compared with patients with other inflammatory diseases. Foell and his colleagues study in 2003, showed significant higher S100A12 levels in patients with active arthritis (RA, psA) than healthy controls. Our results showed non-significant difference of MRP8/MRP14 between group I (RA) and II (PsA), These results were in accordance with Kane et al. (2003), they reported that MRP8/MRP14 were equally increased in PsA, RA and spondyloarthritis patients. Foell and his colleagues in 2003 found S100A12 serum levels were highest in RA, markedly elevated in PsA and less but still significantly elevated in seronegative arthritis compared with healthy controls.

Our results showed a significant positive correlation of MRP8/MRP14 and S100A12 as well as SF MRP8/MRP14 and SF S100A12 of group I (RA) with systemic parameters of disease activity (ESR, CRP and DAS). These results were similar to An et al. (2005) who concluded that MRP8/MRP14, serum amyloid A1 and A2 (SAA1/SAA2) and ubiquitin may play important roles in development of RA and their determination may benefit early diagnosis, evaluation of disease activity and investigation of new therapy targets.

Also; these results were similar to Kan et al. (2003) who found a significant correlation of MRP8/MRP14 and S100A12 of RA and PsA serum with systemic parameters of disease activity (ESR and CRP). They didn't investigate its correlation with disease activity score (DAS), which depends mainly on the ESR as

reported by Makinen and his colleagues in 2007 that ESR had the greatest effect on the components of DAS28 (tender joint count, patient's general health and swollen joint count) score. Once the MRP8/MRP14 and S100A12 were correlated with ESR; consequently it is correlated with DAS.

Our results showed a positive significant correlation of S100A12 both in serum and synovial fluid in RA patient with systemic parameters of disease activity scores (ESR, CRP and DAS). These results were similar to Foell et al., 2003 and Foell et al., 2007.

Our results showed a significant correlation of MRP8/MRP14 and S100A12 both in serum and SF in RA patients with the intra-articular activity markers as WBCs, lymphocytes and A-SAA. It was in contrast to Kan et al. (2003) as regard the correlation of MRP8/MRP14 in the serum but was similar to them as regard synovial level correlation with the local inflammatory parameters; where they reported a significant correlation of SF MRP8/MRP14 (and not its serum level) with local parameters of disease activity (WBCs, lymphocytes and acute phase serum amyloid A).

In our study, the correlation of SF MRP8/MRP14 and SF S100A12 with systemic disease activity parameters and MRP8/MRP14 with local inflammatory parameters found to be due to significant correlation of both MRP8/MRP14 and S100A12 in the serum and synovial fluid consequently both correlates with the systemic and local inflammatory parameters .On the other hand, Kane and his colleagues results in 2003; showed no significant differences in their levels in serum and synovial fluid with higher level in synovial so the serum level correlates with the systemic parameters and the synovial level correlates only with the local inflammatory parameters and not with systemic one.

Our results showed a positive significant correlation of serum level of MRP8/MRP14 and S100A12 in RA patients with its synovial level and this was similar to Frosch et al. (2000), Foell et al.(2003) and Foell et al. (2007) they found a correlation between serum and synovial level in patients with RA and PsA. On the other hand it was contrary to Kane et al. (2003) who found that, serum level of MRP8/MRP14 didn't correlate with its synovial level and even higher level of MRP8/MRP14 were found in SF of patients with RA and PsA; their explanation were made on the base of lesser contribution of MRP production by a single knee joint to the serum concentration in polyarticular disease.

The serum and synovial fluid of MRP8/MRP14 and S100A12 in our study showed non-significant correlation with morning stiffness, swollen joint count and RAI in RA patients and this was similar to

Makinen et al. (2007) where they considered ESR is the main factor for disease activity score.

The results of MRP8/MRP14 and S100A12 in the PsA serum showed a positive significant correlation with ESR, CRP, DAS and PASI; these results were similar to (Brun et al., 1994, Hammer et al., 1995 and Kane et al., 2003), they found significant correlation of serum level with the systemic parameters of disease activity (ESR and CRP). On the other hand, Benoit and his colleagues in 2006; found an elevation of serum levels of S100A8 and S100A9 in PsA compared to healthy control; which was correlated with the disease activity as reflected by the psoriasis area and severity index (PASI).

These data demonstrate that hyper-proliferation and abnormal differentiation of psoriatic skin is associated with a massive up-regulation and secretion of S100A8, S100A9 and S100A12, suggesting not only a prominent role of these molecules during intracellular calcium–dependent signaling but also implying distinct extracellular functions. Being into consideration that DAS proved to be considerably different in PsA compared with RA, therefore its application for disease activity assessment in patients with PsA is not recommended (Leeb et al., 2007). Also, the results of this study showed non-significant correlation of MRP8/MRP14 and S100A12 in group II PsA with morning stiffness, RAI and swollen joint count; these were partially similar to Kane et al. (2003) who found no significant correlation of MRP8/MRP14 with swollen joint count, but they found a significant correlation of it with RAI which was in contrast to our results, also they didn't study the correlation with morning stiffness.

Our results showed a significant correlation of SF MRP8/ MRP14 and SFS100A12 with local inflammatory markers (WBCs, lymphocytes and A-S AA). Also, the SF MRP8/MRP14 and SF S100A12 in group II showed non-significant correlation with morning stiffness, swollen joint count, RAI, ESR, CRP, DAS, PASI, MRP8/MRP14 and S100A12 in the serum; this was in accordance to Kane et al. (2003) who found that, no significant correlation between SF MRP8/MRP14 in PsA patients with any of the systemic parameters of activity or with the serum level of MRP8/MRP14 or S100A12 and only showed a significant correlation with the local inflammatory parameters in the synovial fluids.

Conclusions:
MRP8/MRP14 and S100A12 in the serum can be used to monitor systemic disease activity while, SF MRP8/MRP14 and SF S100A12 can be used to monitor local inflammatory markers. Being correlated

with disease activity parameters, can be used to monitor disease activity and response to treatment.

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