Pathogenetic Role of Matrix Metalloproteinase-2 and Matrixmetalloproteinase-9 in Behcet's Disease

Sahar S Ganeb[1], Howyda M Kamal[2] and Ayser A Fayed[3]

Rheumatology, Rehabilitation & Physical Medicine[1], Clinical & Chemical Pathology[2] and Ophthalmology[2] Departments, Benha University, Faculty of Medicine, Egypt
sahar_ganeb@yahoo.com

Abstract: Objective: To assess serum levels of Matrix metalloproteinases-2 (MMPs-2) and MMP-9 in Behcet's disease (BD) patients to investigate the possible association between MMP-2 and MMP-9 serum levels with clinical manifestations and disease activity. Methodology: Thirty BD patients and 30 age and sex matched healthy controls were included. Thorough clinical examination with stress on dermatological, locomotor, neurological and ophthalmologic manifestations. Assessment of disease activity was done. We compared the activity scores of patients with their serum levels of MMP2 and MMP-9. Assessment of ESR, CRP, MMP-2 and MMP-9 serum levels by ELISA were performed. Results: A statistical significant increase ($P<0.001$) in MMP-9 levels was found in BD patients in comparison with the control group, while there was non-statistical significant difference ($P>0.05$) in MMP-2 levels in BD patients in comparison with the control group. Within the BD patients' group, there were elevations of MMP-2 and MMP-9 serum levels in BD patients with vascular lesions, CNS lesions and disease activity ($P<0.05$). There were statistical significant positive correlations between MMP-2 and MMP-9 serum levels with disease activity score ($r= 0.425$, $P<0.05$), ($r= 0.413$, $P<0.05$) respectively and vascular lesions ($r = 0.394$, $P<0.05$), ($r = 0.458$, $P<0.05$) respectively. Conclusion: Increased serum levels of MMP-2 and MMP-9 in BD patients can be considered as a pathogenetic marker of BD disease activity. These higher levels correlated with systemic involvement and were associated with various clinical manifestations.

[Sahar S Ganeb, Howyda M Kamal and Ayser A Fayed. **Pathogenetic Role of Matrix Metalloproteinase-2 and Matrixmetalloproteinase-9 in Behcet's Disease.** *Life Sci J* 2012;9(3):706-712] (ISSN:1097-8135). http://www.lifesciencesite.com. 99

Keywords: Behcet's disease, Matrix metalloproteinases, disease activity of Behcet's disease.

1. Introduction

Behcet's Disease is a chronic inflammatory multisystem disorder of unknown disorder characterized by recurrent orogenital ulcers, and skin lesions, ocular involvement which is frequent and sever, often bilateral, rapidly compromising the visual function. Eye lesion have been found including anterior uveitis, posterior segment involvement with vasculitis, vitritis, retinal oedema, and venous occlusion. Eye involvement my also be associated with neurological manifestations like optic neuropathy. The disease frequently occurs in Mediterranean countries, the Middle East, and eastern Asia, there are no pathognomonic laboratory tests or histologic findings specific to BD, thus, the diagnosis is based on clinical criteria, and various criteria have been proposed. The most commonly used criteria are those of the International Study Group for BD, and these require recurrent oral ulceration plus at least two of the following: recurrent genital ulcerations, eye lesions (such as uveitis), skin lesions (such as erythema nodosum or folliculitis), and a positive skin pathergy test (1,2).

MMPs are a large family of proteolytic enzymes involved in an array of physiological and pathological processes from development, morphogenesis, reproduction, wound healing, and aging to inflammation, angiogenesis, neurological disorders, and cancer cell invasion and metastasis (3).

MMPs differ structurally and that each MMP has the ability to degrade a particular subset of matrix proteins. The protein products are, however, classified by shared functional and structural characteristics (4). Based on the substrate specificity, the family of MMP enzymes is subdivided into subgroups such as stromelysins (MMP-3, -10 and -11), collagenases (MMP-1, -8 and -13), gelatinases (MMP-2, and -9) and membrane-type MMPs (MMP-14, -17, -22, -24, -25) (5).

Among these, gelatinases comprised of gelatinase A (MMP-2) and gelatinase B (MMP-9), they have unique ability to degrade the type-IV collagen, a major component of the basement membrane (6). The gelatinases are secreted as zymogens and cleave to the active form and their function is tightly regulated by several different mechanisms (7).

Together, the MMPs are able to process or degrade all the known protein components of the extracellular matrix (ECM) (4,8). They are a family of enzymes that regulate the ECM environment and whose activity has been implicated in normal and pathological processes (9,10). Each ECM element is cleaved by a specific MMP or MMP group (11). Pro-

inflammatory cytokines such as interleukin-1 (IL-1) and tissue necrosis factor-α (TNF-α) have been shown to up-regulate MMP-9 (12,13). MMP-9 is considered to be a key determinant of extracellular matrix degradation, having collagen as the main substrate (14).

MMP-9 appears more likely than MMP-2 to be involved in the pathophysiology of Giant cell arteritis. MMP-9 not only participates in the degradation of elastic tissue but also is associated with intimal hyperplasia, subsequent luminal narrowing, and neoangiogenesis (15).

Aim of the work:

The present study aimed to assess the serum levels of MMP-2 and MMP-9 in Behcet's disease patients, to investigate the possible pathogenetic association between MMP-2 and MMP-9 serum levels with clinical manifestations and disease activity.

2. Patients and Methods

Thirty patients, diagnosed as BD according to the international study group criteria (ISGC, 1990) (16), and thirty age and sex matched healthy volunteers serving as a control group were enrolled in this study.

All participants gave informed consent and the local Ethical Committee approved the study.

Exclusion criteria: Patients who had other illnesses that might affect the results of the study, such as other autoimmune diseases, herpes simplex, renal, hepatic diseases or diabetic patients were excluded from the study.

All BD patients were subjected to the following: detailed history taking, thorough clinical examination with stress on dermatological, locomotor, neurological and ophthalmological disorderd , assessment of disease activity was done at time of blood sampling according to the Leeds activity score system (17). Patients with BD were categorized as active (total activity score ≥5) or inactive (total activity score <5).

Laboratory Investigations:

Seven milliliters of venous blood was drawn. One ml on EDTA for complete blood picture by sysmex kx 21. Two mls on Na citrate (with ratio1:4) for ESR estimation by Westergren method recorded in mm/hr.

The remaining blood sample was put in a plain tube, left to clot for 20 mins., then centrifuged at 3000 rpm for 30 mins. The serum was used in the measurement of C-reactive protein (CRP) by the turbidity assay as specified by the manufacturer (Orion diagnostic, cat. No.67977), with an established normal range of (0 - 0.8 mg/dl) and the rest of serum samples were stored at -20°C until measuring MMP-2 and MMP-9 levels by ELISA.

Measurements of MMP-2 and MMP-9:

The levels of MMP-2 was measured by human MMP-2 ELISA cat.No: BBT0459R manufactured by (Biovendor laboratorni medicina a.s). Sensitivity <10 pg/ml. Concentrations of unknown samples were determined from a curve obtained by the standards.

MMP-9 was measured by human MMP-9 ELISA cat. No. RBMS2016/2R manufactured by (Biovendor laboratorni medicina a.s). The detection limit was ≤ 0.05 ng/ml, with inter-assay and intra-assay coefficient of variation (CVs) were 10.2% and 7.3% respectively.

Statistical analysis:

The collected data were presented and analyzed using SPSS version 17 soft ware. Suitable statistical techniques were calculated as number and percent or mean and standard deviation. Student "t" test, was used as a test of significance and 95% CI. The relationship between the variables was evaluated by Spearman's correlation.

3. Results

This study included 30 patients, 19 males (63.3%) and 11 females (36.6%). Their ages ranged from 21-51 years with a mean of 37.52±7.74 years. Thirty age and sex matched healthy volunteers serving as a control group- 18 males (60%) and 12 females (40%), aged from 21-53 years with a mean of 33.29±9.82 years were included in this study. Patients' disease duration ranged from 2 to 11 years with a mean of 5.73±3.5 years.

Patients were taking corticosteroids and/or immunosuppressive agents in variable doses.

Table (1) Shows clinical manifestations of BD patients: Skin lesions: erythema nodosum, sterile pustules or papules in 13 patients (43.3%). Arthritis in 14 patients (46.6%). Ocular disorders in 13 (43.3%): uveitis in 11 patients (36,7%), optic neuritis in one eye (3.3 %) and retinal vasculitis in one patient (3.3%) (figure 1) displayed a picture of optic neuritis (a) and a fluorescein angiography of a case of retinal vasculitis (b) . Vascular lesions in 5 patients (16.6%): venous thrombosis in 4 patients (13.3%) and arterial thrombosis in one patient (3.3%) were encounterd, and 50% of patients had disease activity.

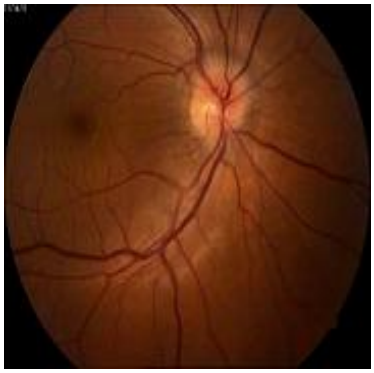
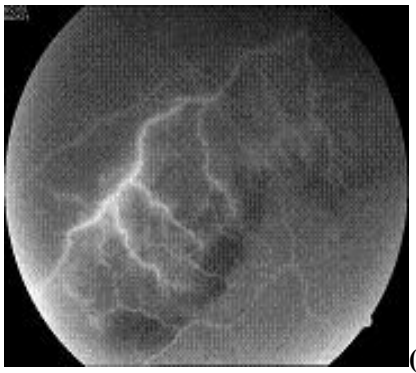
(a)   (b)

Figure [1] : a picture of optic neuritis (a) ,a fundus fluorescein angiography of a case of retinal vasculitis (b)

Table (1): Clinical manifestations of BD patients (no=30).

Clinical manifestations	No of patients	Percentage
Oral aphthous ulcers	18	60%
Genital ulcers	8	26.6%
Skin lesions	13	43.3%
Arthritis	14	46.6%
Ocular manifestations	13	43.3%
Vascular lesions	5	16.66%
CNS manifestations	2	6.6%
Disease activity	15	50%
+ve skin Pathergy test	8	26.6%

Table (2): Shows that there was no statistical significant difference (P>0.05) in MMP-2 levels in BD patients in comparison with the control group, while the levels of MMP-9 were significantly higher (P<0.001) in BD patients in comparison with control group.

Table (2): ***ESR, CRP and serum MMP-2 and MMP-9 levels in patients and controls.***

Parameters	Patients mean±SD Number=30	Controls mean±SD number=30	t	P	95% CI
ESR	39.59±15.63	14.57±5.52	8.3	<0.001*	18.9-31.1
CRP	9.9±5.3	0.4±0.2	9.8	<0.001*	7.6 - 11.4
MMP-2 ng/ml	7.1±5.3	5.14±3.51	1.69	>0.05	0.4 -4.3
MMP-9 ng/ml	36.48±16.43	18.74±12.12	4.76	<0.001*	10.3-25.2

P<0.05*= significant **P>0.05**= nonsignificant

The association between individual clinical manifestations and serum MMP-2 levels revealed significant elevation of MMP-2 serum levels in BD patients with skin lesions, vascular lesions, CNS lesions and disease activity (P<0.05), while there were no association between serum MMP-2 levels and oral ulcers, genital ulcers, arthritis, ocular lesions or a positive skin Pathergy test (P> 0.05), (table 3).

Table (3): Serum MMP-2 in patients with different clinical Manifestations compared to those without in BD patients (no=30).

	Oral ulcers (no18)	Genital ulcers (no=8)	Skin lesions (no=13)	Arthritis (no=14)	Occular lesions (no=13)	Vascular lesions (no=5)	CNS lesions (no=2)	Disease activity (no=15)	+ve Pathergy (no=8)
With	6.92±2.8	7.34±5.1	7.34±2.6	6.28±4.1	6.85±4.7	12.19±2.7	10.22±4.1	7.71±2.9	6.78±4.7
without	6.83±2.1	6.31±2.7	5.48±1.4	5.91±3.2	6.37±3.9	5.21±1.9	5.43±2.3	5.33±2.1	6.14±4.1
t	0.094	0.72	2.52	0.28	0.3	7.01	2.74	2.57	0.36
P	0.92	0.47	0.019*	0.78	0.76	0.0000*	0.01*	0.016*	0.72

P<0.05*= significant P>0.05= non significant

Table (4): Shows that MMP-9 serum levels were significantly elevated in BD patients with skin lesions, ocular lesions, vascular lesions, CNS lesions and disease activity (P<0.05), while there were no increase in MMP-9 serum levels with oral ulcers, genital ulcers, arthritis or a positive skin Pathergy test (P> 0.05).

Table (4): Serum MMP-9 in patients with different clinical Manifestations compared to those without in BD patients (no=30).

	Oral ulcers (no=18)	Genital ulcers (no=8)	Skin lesions (no=13)	Arthritis (no=14)	Occular lesions (no=13)	Vascular lesions (no=5)	CNS lesions (no=2)	Disease activity (no=15)	+ve Pathergy (no=8)
With without t t P	38.93±10.1 37.85±11.2 0.27 0.79	39.52±19.7 36.67±14.5 0.43 0.66	38.99±7.01 34.01±5.01 2.17 0.83	38.39±15.8 35.16±15.3 0.56 0.57	39.97±10.3 32.13±9.82 2.12 0.042*	45.21±13.4 31.78±10.4 2.52 0.018*	48.64±15.3 30.31±11.8 2.1 0.045*	46.93±31.8 26.76±16.5 2.18 0.037*	38.16±13.2 34.84±8.40 0.82 0.42

P<0.05*= significant **P>0.05**= non significant

The present work demonstrates that in the correlation between serum MMP-2 levels and different clinical and laboratory parameters among BD patients, there was statistically significant positive correlation with disease activity score (r = 0.3425, P<0.05) figure (2) and vascular lesions (r = 0.394, P<0.05).

Correlating between MMP-9 serum levels and some variables among BD patients showed statistically significant positive correlations with disease activity score (r = 0.413, P<0.05) (figure 3) and vascular lesions (r = 0.458, P<0.05).

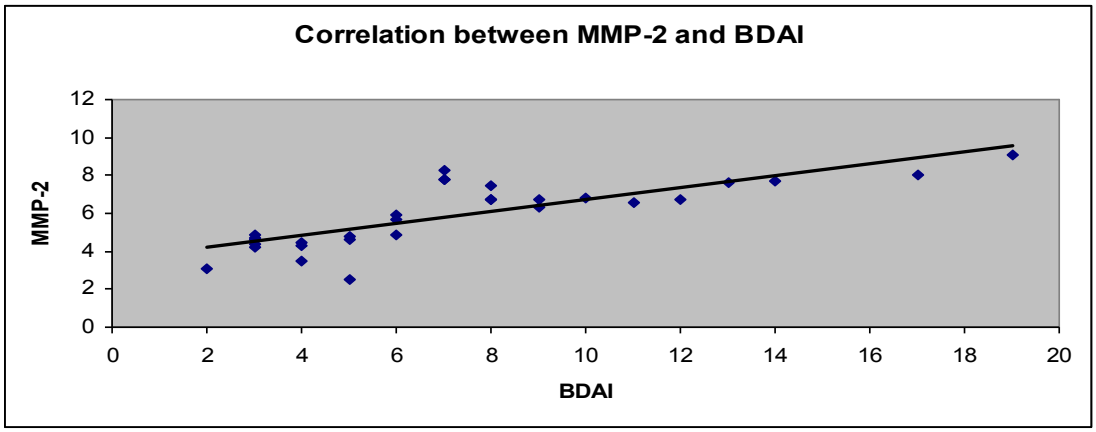


Figure [2]

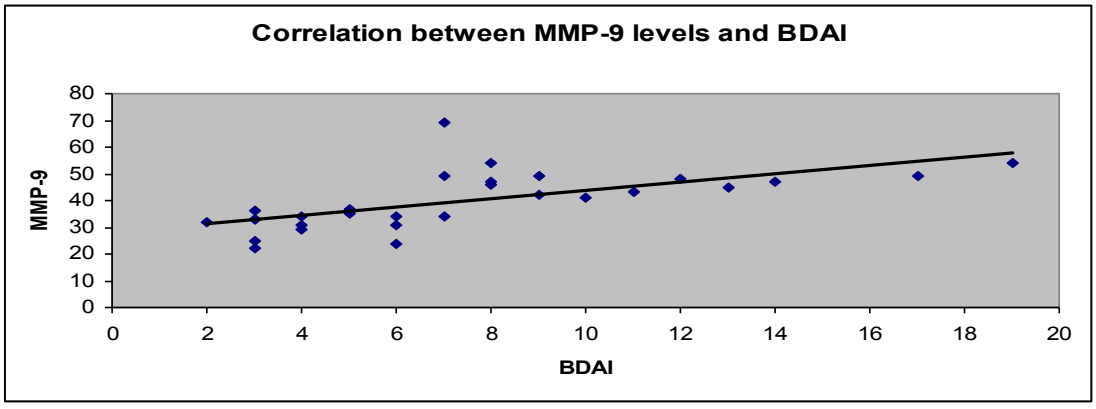


Figure [3]

4. Discussion

Behçet's disease (BD) is a chronic systemic inflammatory disorder affecting multiple organs with a generalized vasculitis (18). It is also described as the triad of recurrent oral and genital ulcers, iritis with hypopyon, retinal vasculitis and posterior uveitis , primarily affecting young adults aged 25–35 years (1,19,20).

Aksoy et al. (2011) (21), reported that the numbers of BD patients suffering from individual clinical manifestations of the disease to varying degrees were as follows: 56% oral ulceration, 40% genital ulceration, 32% ocular involvement, 40% vascular involvement, 40% arthritis/arthralgia and 48% cutaneous lesions, such as erythema nodosum and papulopustular eruption. These results were comparable to our study.

Pandrea et al. (2007) (22), reported that vascular lesions affect 7–29% of BD patients at least once during the clinical course of the disease.

Almost 90% of their patients were diagnosed with superficial thrombophlebitis, and up to 35% developed major thromboembolic complications involving the superior and/or inferior vena cava, arteries were less frequently involved (23).

In this study, the serum levels of MMP-2 showed non statistical significant difference ($P>0.05$) in BD patients in comparison with the control group. On the other hand, the serum levels of MMP-9 were significantly higher ($P<0.001$) in BD patients in comparison with the control group. These results were in accordance with those reported by Pay et al., (2007) (24).

In the current study the association between individual clinical manifestations and serum MMP-2 levels revealed elevation of MMP-2 serum levels in BD patients with skin lesions, vascular lesions, CNS lesions and disease activity ($P<0.05$).

Pay et al., (2007) (24), in their study on 58 BD patients found that the serum levels of both MMP-2 and MMP-9 in patients with systemic involvement, vascular involvement, thrombotic involvement and aneurysm formation were higher than those of healthy controls. Also, they found that the serum level of MMP-9 in patients with ocular disease was higher than those of healthy controls. Therefore, they proposed that MMP-2 and MMP-9 may play a pathogenic role in vasculo-Behçet's disease complicated with aneurysm formation. These results are in accordance with our findings where MMP-9 serum levels were significantly elevated in BD patients with, ocular, vascular and CNS lesions and with disease activity ($P<0.05$).

Also, Pay et al., (2007) (24) stated that serum levels of MMP-2 and MMP-9 were not found different compared to those with mucocutaneous involvement. This coincides with our results as there were no association between serum MMP-2 and MMP-9 levels and oral ulcers or genital ulcers. On contrary to their study our results showed significant elevation of MMP-2 and serum levels in BD patients with skin lesions.

Lorelli et al. (2002) (25), demonstrated that the plasma MMP-9 levels were higher in the patients with abdominal aortic aneurysm compared with healthy patients. The causes of aneurysms were either atherosclerosis and/or degeneration (26). This supports our finding, as there were significant increase MMP-9 serum levels in patients with vascular lesions.

Vascular involvement in Behçet syndrome is most likely to involve thrombosis in the venous system, but arterial lesions are associated with greater risks (20,23). The pathogenesis is considered to be vasculitis resulting in obliterative endarteritis of the vasa vasorum supplying the medium and large vessels, the overall mortality in Behçet syndrome is 3%–4%, and the most common cause of death is aneurysmal rupture (19,27).

Studies on a possible association between the occurrence of thrombosis and thrombophilia in patients with BD are controversial, Venous and arterial thrombosis occur in patients with this disease and are associated with significant morbidity and mortality, (28). Because of their ability to destroy elastin, MMP-2 and -9 have been hypothesized to play a primary role in the internal elastic lamina degradation (15).

Johnson and Galis (2004) (29), demonstrated differential regulation between these MMPs in vivo with regard to smooth muscle cells (SMCs) migration and cell-mediated collagen organization and they reported: whereas MMP-2 and MMP-9 may have similar matrix-degrading abilities, only MMP-9 appears to play an additional role in SMC attachment to the matrix, this may help in tissue remodeling.

This study revealed that there were no association between MMP-9 serum levels and positive skin Pathergy test ($P> 0.05$), this result agreed with the study of Aksoy et al., (2011) (21) who found no association between MMP-9 serum levels and BD group with the presence of a positive pathergy test.

Senzaki et al.,(2001) (30) demonstrated that levels of MMPs including MMP-2 and MMP-9 were significantly higher in patients with Kawasaki disease as compared to controls, and with the levels of MMP-9 in Kawasaki disease patients with coronary artery lesion being higher than those without coronary artery lesion. Takeshita et al., (2001) (31) revealed that MMP-9 was generated from circulating leukocytes. Matsuyama et al., (2003) (32) reported that the levels

of MMP-2 and MMP-9 were higher in patients with Takayasu arteritis than in controls, but only MMP-9 was found to be correlated with disease activity score.

The present work demonstrates that in the correlation between both serum MMP-2 and MMP-9 levels and different clinical and laboratory parameters among BD patients, there were statistical significant positive correlations with disease activity score and vascular lesions.

In accordance with the current literature, Pay et al., (2007) (24) found that MMP-2 and MMP-9 had statistical significant correlations with BD activity score and they concluded that serum MMP-2 and MMP-9 levels can be used as an activity indicator for vasculo-Behçet's or active Behçet's patients, respectively.

On the contrary, Aksoy et al. (2011) (21) revealed that plasma levels of MMP-9 did not display a positive correlation with BD activity index scores.

Conclusion: Increased serum levels of MMP-2 and MMP-9 in BD patients can be considered as a pathogenetic marker of disease activity. These levels correlated with systemic and vascular involvement, so their assessment would most likely help to improve the clinical outcome of patients affected with this disease.

Acknowledgments:

We thank Prof Dr Samia Abdelmoneim for her unbound assistance throughout this work.

Disclosure statement: The authors have declared no conflicts of interest.

Corresponding author
Sahar S Ganeb
Rheumatology, Rehabilitation & Physical Medicine
Faculty of Medicine, Benha University,,Egypt
sahar_ganeb@yahoo.com

References

1-Bouarhroum A, Sedki N, Bouziane Z, El Mahi O, El Idrissi R, Lahlou Z, Lekehel B, Sefiani Y, El Mesnaoui A, Benjelloun A, Ammar F and Bensaïd F (2006): Extracranial carotid aneurysm in Behçet disease: Report of two new cases. Journal of vascular surgery; 43(3): 627-630.

2-Gassoux N, Fardeau C, Le Hoang P, (1999): Manifestations ocularires de la maladie de Behcet. Ann Med Inteme;150:529-34.

3-Muroski ME, Roycik MD, Newcomer RG, Van den Steen PE, Opdenakker G, Monroe HR, Sahab ZJ and Sang QX (2008): Matrix metalloproteinase-9/gelatinase B is a putative therapeutic target of chronic obstructive pulmonary disease and multiple sclerosis. Curr Pharm Biotechnol; 9(1):34-46.

4-Rajendran R, Rajeesh Mohammed PK, Saleem Shaikh, Shanthi and Pillai MR (2006): Expression of matrix metalloproteinases (MMP-1, MMP-2 and MMP-9) and their inhibitors (TIMP-1 and TIMP-2) in oral submucous fibrosis. Indian Journal of Dental Research; 17 (4): 161-166.

5-Nagase H and Woessner j F (1999): Matrix metalloproteinases. J. Biol. Chem; 274: 21491-4.

6-Shah FD, Shukla SN, Shah PM, Shukla HK and Patel PS (2009):Clinical significance of matrix metalloproteinase 2 and 9 in breast cancer. Indian Journal of Cancer; 46(3):194-202.

7-Strenlicht MD and Werb Z (2001): How matrix metalloproteinases regulate cell behavior. Ann Rev cell Dev Biol; 17:463-516.

8-Ahmed MM and Mohammed SH (2011): Matrix metalloproteinases 2 and 9 *in situ* mRNA expression in colorectal tumors from Iraqi patients. Indian Journal of Pathology and Microbiology; 54(1): 7-14.

9-Nagase H, Visse R and Murphy G (2006): Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res; 69:562-73.

10-Murphy G and Nagase H (2008): Progress in matrix metalloproteinase research.Mol Aspects Med; 29:290-308.

11-Visse R and Nagase H (2003): Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res; 92:827-39.

12-Kovanen PT, Kaartinen M and Paavonen T (1995): Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. Circulation; 92: 1084–1088.

13-Saren P, Welgus HG and Kovanen PT (1996): TNF-alpha and IL-1beta selectively induce expression of 92-kDa gelatinase by human macrophages. J Immunol; 157: 4159–4165.

14-Garvin P, Nilsson L, Carstensen J, Jonasson L, and Kristenson M **(2008):** Circulating Matrix Metalloproteinase-9 Is Associated with Cardiovascular Risk Factors in a Middle-Aged Normal Population. PLoS ONE; 3(3): e1774.

15-Rodríguez-Pla A, Bosch-Gil J, Rosselló-Urgell J, Huguet-Redecilla P, Stone JH and Vilardell-Tarres M (2005): Metalloproteinase-2 and -9 in Giant Cell Arteritis. Circulation; 112:264-269.

16-International study group for Behcet's disease (1990): criteria for diagnosis of Behcet's Disease, Lancet; 335:1078-1080.

17-Bhakta BB, Brennan P, James TE, Chamberlain MA, Noble BA and Silman AJ (1999): Behcet's disease: evaluation of a new instrument to measure clinical activity. Rheumatology; 38:728–733.

18-Rizzi R, Bruno S, and Dammacco R (1997): "Behc¸ et's disease: an immune-mediated vasculitis involving vessels of all sizes," International Journal of Clinical and Laboratory Research; 27:225-32.
19-Safar HA, Khamseen SA, Kansou J, Abubacker S, Francis I and Asfar S (2005): Vascular aneurysms in Behcet's disease. Surg Pract; 9:35–40.
20-Uzun L, Ugur MB, Ulukent SC, Ozdemir H and Koca R (2005): Vasculo-Behcet's disease mimicking a metastatic neck mass. Tohoku J Exp Med; 206:81–4.
21-Aksoy Y, Ercan A, Dalmizrak O, Canpinar S, Durmazlar S and Bayazit M (2011): The determination of matrix metalloproteinase 9 activity and gene expression levels in Behcet's disease patients with aneurysmal complications. Clin Rheumatol; 30: 515–519.
22-Pandrea A, Rudinskaya A, Klein B and Krebs T (2007): What does it take to diagnose Behçet disease? J Clin Rheumatol; 13:31–4.
23-Al-Basheer M and Hadadin F (2007): Aneurysm formation type of vasculo-Behcet's disease. Heart Lung Circ; 16:407–9.
24-Pay S, Abbasov T, Erdem H, Musabak U, Simsek I, Pekel A, Akdogan A, Sengul A, and Dinc A **(2007):** Serum MMP-2 and MMP-9 in patients with Behçet's disease: do their higher levels correlate to vasculo-Behçet's disease associated with aneurysm formation?. Clin Exp Rheumatol; 25 (4 Suppl 45):S70-5.
25-Lorelli DR, Jean-Claude JM, Fox CJ et al. (2002): Response of plasma matrix metalloproteinase-9 to conventional abdominal aortic aneurysm repair or endovascular exclusion: implications for endoleak. J Vasc Surg; 35(5):916–922.
26-Takagi H, Manabe H, Kawai N et al. (2009): Circulating matrix metalloproteinase-9 concentrations and abdominal aortic aneurysm presence: a meta-analysis. Interact Cardiovasc Thorac Surg; 9 (3):437–440.
27-Kwon Koo B, Shim WH, Yoon YS, Kwon Lee B, Choi D, Jang Y, et al. (2003): Endovascular therapy combined with immunosuppressive treatment for pseudoaneurysms in patients with Behcet's disease. J Endovasc Ther; 10:75–80.
28-Leiba M, U Seligsohn, Y Sidi, D Harats, B Sela, J Griffin, A Livneh, N Rosenberg, I Gelernter, H Gur, and M Ehrenfeld (2004): Thrombophilic factors are not the leading cause of thrombosis in Behçet's disease Ann Rheum Dis. November; 63(11): 1445–1449.
29-Johnson C and Galis ZS (2004): Matrix metalloproteinase -2 and -9 differentially regulate smooth muscle cell migration and cell-mediated collagen organization. Arterioscler Thromb Vasc Biol; 24: 54–60.
30-Senzaki H, Masutani S, Kobayashi J et al. (2001): Circulating matrix metalloproteinases and their inhibitors in patients with Kawasaki disease. *Circulation*; 104: 860-3.
31-Takeshita S, Tokutomi T, Kawase H et al. (2001): Elevated serum levels of matrix metalloproteinase- 9 (MMP-9) in Kawasaki disease. Clin Exp Immunol; 125: 340-4.
32-Matsuyama A, Sakai N, Ishigami M et al. (2003): Matrix metalloproteinases as novel disease markers in Takayasu arteritis. Circulation; 108: 1469-73.

6/21/2012