

Association between Serum Myeloperoxidase And Cardiovascular Risk Factor In Psoriatic Children In Damietta Governorate

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Abstract: MPO is often released from stimulated polymorphonuclear leukocytes at sites of inflammation and is involved in the generation of reactive oxygen and nitrogen species and tissue damage. Thus, it can play a role of inflammatory skin disease such as psoriasis and subsequent development of cardiovascular comorbidities associated with psoriasis. **Aim of the work:** to examine the association between serum myeloperoxidase and cardiovascular risk factor in psoriatic children in Damietta governorate. Fifty psoriasis children and fifty age and sex matched controls were recruited from pediatric and dermatology clinics at Al-Azhar University Hospital (New Damietta), Egypt. All were submitted to full history taking, clinical examination and laboratory investigation with measurement of myeloperoxidase serum levels. **Results** of the present study showed that, there was significant increase of traditional risk factors for cardiac disease in study group when compared to control group. In addition, MPO was significantly increased in psoriasis patients (pointing to possible role in pathogenesis of psoriasis). However, there was no significant correlation between MPO and risk factors of psoriasis. On the other hand, there was significant positive correlation between MPO and duration of disease at the first followed by severity of the disease. **Conclusion:** MPO played a role in pathogenesis of psoriasis. But, MPO do not play a role in development of CVD in children with psoriasis.

[Mohamed A. Salam; Zakaria Mahran, Tarek Emran and Hammouda Abdul khalik. **Association between Serum Myeloperoxidase And Cardiovascular Risk Factor In Psoriatic Children In Damietta Governorate.** *J Am Sci* 2015;11(7):100-105]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>. 12

Keywords: myeloperoxidase, psoriasis, cardiovascular, children

1. Introduction

Psoriasis is autoimmune, chronic inflammatory disease. It affects ~ 2-3% of the world's population, including 125 million people worldwide. Psoriasis had a negative impact on health-related quality of life. This effect is comparable to those of other major medical and psychiatric diseases, such as myocardial infarction (MI), type 2 diabetes mellitus, hypertension and depression. One of the major consequences of psoriasis is its association with cardiovascular diseases (CVDs) and established cardiovascular (CV) risk factors (**Cao et al., 2014**). Initial studies indicated that psoriasis may be associated with increased prevalence of CVDs (e.g., MI, CHF and stroke), as well as CV-related mortality. However, **Gelfand et al. (2006)** reported that psoriasis may provide an independent risk for MI, even after adjusting for established CV risk factors, especially in young patients with severe psoriasis.

The association between psoriasis and cardiovascular disease may be explained by sharing chronic systemic inflammatory processes. In addition, the chronic inflammation characteristic of psoriasis is central to the pathophysiology of atherosclerotic plaque initiation, progression and rupture which lead to acute thrombotic events (**Rhew and Ramsey-Goldman, 2006**). Furthermore, studies with

psoriasiform animal models have also established that sustained skin-specific inflammation is associated with increased aortic root vascular inflammation and arterial thrombosis (**Wang et al., 2012**).

Myeloperoxidase (MPO) is a pro-oxidative and proinflammatory hemeprotein stored in granules of leukocytes and secreted upon cellular activation following inflammation (**Klebanoff, 2005**). It was first discovered as an iron-containing protein from extracts from human leukocyte-rich purulent discharge by **Agner (1941)**. Initially, MPO was named "verde-peroxidase" based on its vivid green color, but subsequently, the prefix "verde" was replaced with the term "myelo" upon discovering its expression in myeloid lineages of hematopoiesis (**Klebanoff, 2005**). The synthesis of MPO begins in the promonocytes and promyelocyte stages of hematopoiesis and is commonly found in mature neutrophils, in monocytes, and in some types of tissue macrophages. The physiological role of MPO appears to be a critical component of phagocytic microorganism-killing activities of the innate immune system. In fact, MPO accounts for as much as 5% of the total dry mass in human leukocytes (**Hansson et al., 2006**).

In addition, MPO catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite—a

strong reactive oxygen species (ROS, 95% of circulating MPO in healthy individuals derives from polymorphonuclear neutrophils. Emerging evidence in humans consistently suggest that MPO may not merely be a marker for CVDs, but that MPO-induced oxidative stress and inflammation may actively contribute to the formation, progression and destabilization of atherosclerotic plaques which lead to acute coronary syndromes (ACS) (Castellani *et al.*, 2006).

MPO is often released from stimulated polymorphonuclear leukocytes at sites of inflammation and is involved in the generation of reactive oxygen and nitrogen species and tissue damage (Shiba *et al.*, 2008). Thus, we hypothesized that, as prooxidative and proinflammatory protein, MPO may play a role in the pathogenesis of psoriasis in children; and we designed the present study to explore this hypothesis.

Aim of the work

The present study was designed to examine the association between serum myeloperoxidase and cardiovascular risk factor in psoriatic children in Damietta governorate.

2. Patients and methods

Fifty psoriasis children and fifty age and sex matched controls were recruited from pediatric and dermatology clinics at Al-Azhar University Hospital (New Damietta), Egypt. Control patients did not have psoriasis or any other inflammatory skin disorders (e.g., acne, atopic dermatitis, contact dermatitis, etc...) or any inflammatory disorders in general. All patient guardians provided informed consent to participate in this study after study protocol was explained and before initiation of the study.

All included children were submitted to full history taking which included the following: socio-demographic information, smoking history, allergies, current medications and treatments, lifetime treatments for psoriasis, personal and family medical history especially of psoriasis and psoriatic arthritis (PsA) and cardiovascular diseases (CVDs). In addition, at the study visit, anthropometric measures were obtained. They included included height, weight, waist circumference (WC) measured at the level of the anterior superior iliac spines, and hip circumference measured at the level of the largest circumference around the buttocks. Psoriasis patients were additionally evaluated by measuring their psoriasis area and severity index (PASI).

Echocardiography: All the study population underwent a transthoracic examination. Using M-mode echocardiography, long-axis measurements were obtained at the level distal to the mitral valve leaflets according to the recommendations of the

American Society of Echocardiography. Pulse wave Doppler measurements of aortic and trans-mitral valve flow profiles were obtained. The trans-mitral flow velocity was measured using pulse wave Doppler with the sample volume positioned between the mitral leaflet tips during diastole. Early diastolic flow, atrial contraction signal, early diastolic flow/atrial contraction signal (E/A), and deceleration time (DT) were measured. Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal. Values were measured on three separate beats and then averaged for all parameters.

Pulmonary artery systolic pressure was calculated from tricuspid insufficiency flow in parasternal short axis and apical four chamber view, and the highest tricuspid regurgitation velocity was taken as a study sample. PASP above 30 mmhg was exclusion criteria. The Left ventricular end-systolic volume, end-diastolic volume, fractional shortening and LV ejection fraction were measured from parasternal and apical two and four chamber views, standard views according to recommendations of American Society of Echocardiography.

Serum analyses: A venous blood sample after at least an 8-hour fast was obtained from each patient at the study visit. MPO was quantified with a commercial sandwich enzyme-linked immunosorbent assay (ELISA) kit (LEGEND MAX™, BioLegend, San Diego, USA) according to the manufacturer's recommendation. All sera were tested in duplicate, and results were expressed as the mean values (ng/mL) by using a standard curve. In addition, LDL, HDL, total cholesterol, triglyceride, fasting blood glucose, creatinine and blood urea nitrogen (BUN) were quantified by the clinical laboratory of Al-Azhar University hospital (New Dameitta).

Statistical analysis of data: the collected data organized, tabulated and statistically analyzed using statistical package for social science (SPSS) version 16 (SPSS Inc. USA). Quantitative data were expressed as mean and standard deviation (SD) and categorical data expressed as relative frequency and percent distribution. Unpaired (t) and Chi square tests were used for comparison between groups. For correlation between different variables, the Pearson's correlation coefficient (r) was calculated, and p value ≤ 0.05 was considered significant.

3. Results

In the present work, both study and control groups were matched for age, sex history of previous heart attacks; family history of heart attacks, family history of stroke, blood urea and creatinine (i.e., there was no significant difference between both groups). On the other hand, there was significant increase of

BMI, W/H ratio, blood pressure, fasting blood glucose, LDL, total cholesterol and triglycerides; and significant decrease of HDL in study group when compared to control group. Furthermore, there was significant increase of MPO in study group when compared to control group (2538.96±324.47 vs 1360.60±234.58 respectively). Finally, echocardiographic examination showed non-significant difference between psoriasis and control groups except significant increase of both deceleration time (DT) (196.0±2.08 vs 177.32±1.96 msec respectively) and isovolumetric relaxation time (IVRT) (93.92±2.67 vs 83.48±2.29 respectively). (Table 1).

In the present study, PASI ranged from 3.60 to 15.0 with a mean of 8.01±1.62; while disease

duration ranged from 6 months to 6 years with a mean of 2.35±1.16 years; 76% of cases were of plaque type and 16% of cases had associated psoriatic arthritis (Table 2).

In the present work, there was positive (proportional), mild, significant correlation between MPO levels and PASI score; while there was proportional powerful significant correlation between MPO and duration of disease; and moderate negative between MPO and IVRT. On the other hand, no significant correlation was found between MPO and age, BMI, w/h ratio, fasting blood sugar, or any of lipid profiles or kidney function tests (Table 3; figure 1).

Table (1): Comparison between study and control groups as regard clinical and laboratory data

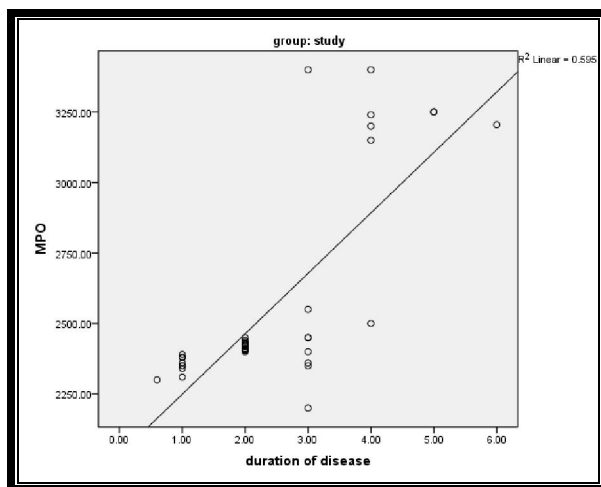
Variable	Study group	Control group	Test	P value
Age	12.44±1.34	12.40±1.39	0.14	0.88(NS)
Male gender	22(44.0%)	27(54.0%)	1.0	0.31(NS)
History of previous heart attack	2(4.0%)	0 (0.0%)	2.04	0.15(NS)
Family history of heart attack	10(20.0%)	6(12.0%)	1.19	0.27(NS)
Family history of stroke	0(0.0%)	0(0.0%)	0.001	1.0(NS)
BMI	27.97±0.65	26.12±0.59	14.78	0.001*
W/H ratio	0.93±0.012	0.88±0.021	14.99	0.001*
Systolic BP	124.26±4.49	113.80±5.76	10.11	0.001*
Diastolic	81.70±4.35	72.50±4.65	10.20	0.001*
Fasting BS	85.26±2.73	83.70±3.40	2.52	0.013*
LDL	127.32±8.57	117.88±10.14	5.02	0.001*
HDL	55.70±3.60	58.42±3.82	3.66	0.001*
Total cholesterol	193.46±4.10	186.40±7.13	6.06	0.001*
Triglycerides	123.90±3.91	118.84±4.55	5.95	0.001*
Creatinine	0.87±0.12	0.82±0.13	1.88	0.07(NS)
BUN	16.78±2.38	16.50±1.86	0.65	0.51(NS)
MPO	2538.96±324.47	1360.60±234.58	20.81	0.001*
LVEDD(mm)	35.76±2.72	35.04±0.83	1.78	0.08(NS)
LVEDS(mm)	21.56±1.31	21.86±1.39	1.11	0.27(NS)
LVEF(%)	60.86±1.34	61.18±1.40	1.16	0.24(NS)
IVS (mm)	7.89±0.11	7.87±0.16	0.75	0.45(NS)
PW(mm)	7.10±0.58	7.20±0.69	0.78	0.43(NS)
LA diameter (mm)	22.94±1.05	22.86±0.98	0.38	0.69(NS)
E/A	1.28±0.02	1.29±0.016	1.87	0.06(NS)
DT(msec)	196.0±2.08	177.32±1.96	46.17	0.001*
IVRT(msec)	93.92±2.67	83.48±2.29	20.95	0.001*
Diastolic dysfunction(n,%)	3(6.0%)	0(0.0%)	3.09	0.08(NS)

Table (2): Disease severity, duration, type and associated psoriatic arthritis in the study group

Variable	Statistics
PASI	8.01±1.62; 3.60 – 15.0
Disease duration (years)	2.35±1.16; 0.5- 6.0
Plaque psoriasis	38 (76.0%)
Psoriatic arthritis	8 (16.0%)

Table (3): Correlation between MPO and other studied variables in study group

	MPO	
	r	p
Age	-0.08	0.57
BMI	-0.04	0.81
W/H ratio	0.01	0.97
Fasting BG	0.18	0.22
LDL	0.07	0.64
HDL	0.07	0.96
TC	0.06	0.67
TG	-0.11	0.43
Creatinine	0.07	0.63
BUN	0.07	0.64
PASI	0.29	0.041*
Duration of disease	0.77	0.001*
LVEDD	0.009	0.949
LVESD	0.021	0.883
LVEF	0.148	0.304
IVS	0.005	0.975
PW	-0.013	0.928
LAD	0.243	0.089
EA	-0.231	0.107
DT	0.021	0.883
iVRT	-0.36	.009*

**Figure (1): Correlation between disease duration and MPO levels in study group**

4. Discussion

Myeloperoxidase (MPO), a member of the heme peroxidase family, is abundantly expressed in neutrophils and monocytes at sites of inflammation. Under physiological conditions MPO reacts with halides, thiocyanate and nitrite and the corresponding MPO-derived oxidation products play an important role in phagocyte's antimicrobial activity by killing

invading pathogens thereby contributing to host defence (Davies *et al.*, 2008). However, persistent activation of MPO results in elevated levels of reactive chlorine species and MPO-derived oxidants have been linked with neurodegenerative disorders, carcinogenesis, lung disease and respiratory damage, rheumatoid arthritis, kidney damage and atherosclerosis (Yap *et al.*, 2007).

An association between MPO levels and the risk of CVD has first been reported in 2001 (Zhang *et al.*, 2001). Since then, numerous studies have addressed the role of MPO as a circulating inflammatory marker in chronic heart failure (Tang *et al.*, 2007), acute coronary syndrome (ACS) (Ndrepepa *et al.*, 2008; Sawicki *et al.*, 2011), and CAD (Cavusoglu *et al.*, 2007). Besides various prospective and cross-sectional studies examining the relationship between MPO and the presence of atherosclerosis or the risk of future CAD, evidence came up that a certain MPO polymorphism in the promoter region (-463G/A) might be associated with CAD (Castellani *et al.*, 2006).

In recent years, the association of psoriasis with several comorbidities, such as obesity, metabolic syndrome (MS), systemic hypertension (SH), dyslipidemia, type 2 diabetes, malignancies, inflammatory bowel diseases, and habits, such as smoking and alcohol abuse has been matter of debate (Christophers, 2007; Gottlieb and Dann, 2009). This association between psoriasis and comorbidities, especially cardiovascular and metabolic disorders, may be related to their chronic and inflammatory nature, especially due to increased pro-inflammatory cytokines that are part of the pathophysiology of such disorders (Kimball and Wu, 2009; Prey *et al.*, 2010).

The present study was designed to examine the association between serum myeloperoxidase and cardiovascular risk factor in psoriatic children in Damietta governorate. Results of the present study showed that, there was significant increase of traditional risk factors for cardiac disease in study group when compared to control group. In addition, MPO was significantly increased in psoriasis patients (pointing to possible role in pathogenesis of psoriasis). However, there was no significant correlation between MPO and risk factors of psoriasis. On the other hand, there was significant positive correlation between MPO and duration of disease at the first followed by severity of the disease.

From these data, it can be said that, MPO played a role in the pathogenesis of psoriasis. However, the present study cannot prove a role of MPO in development of cardiac disease associated with psoriasis.

Consistent with previous reports, our study demonstrated psoriasis patients to be at increased CV

risk with significantly higher WHRs than controls. In addition, psoriasis cases had dyslipidemia than controls. Previous studies have noted that while patients with more severe psoriasis exhibit more lipid abnormalities (i.e., higher total cholesterol, triglycerides), while patients with milder psoriasis may have lower HDL levels as the only detectable lipid abnormality when compared to controls (**Rocha-Pereira et al., 2001; Reynoso-von Drateln et al., 2003**).

In this study we demonstrate a significantly elevated serum MPO level in psoriasis patients when compared to controls. But, we did not find any correlation between W/H ratio or BMI or blood pressure with MPO levels in study group. This is in contradiction with previous studies, which have noted that abdominal visceral fat, and hypertension is associated with elevated systemic MPO levels (**Andelid et al., 2007; Rudolph et al., 2008; de la Sierra and Larrousse, 2009**).

In the present study, we found that serum MPO levels correlate significantly with psoriasis severity as evaluated by PASI. Interestingly, serum MPO levels also associated with the duration for which patients have been diagnosed with psoriasis. These results are in contradiction to those reported by **Cao et al. (2014)** who did not find any association between MPO serum levels with disease duration or severity. This contradiction may be attributed to different ethnic variation or inclusion criteria. In addition, their work was on adult patients while this work included children only.

In the present work we found significant increase of deceleration time and IVRT in study group (psoriasis) when compared to control group. These results are comparable to those reported by **Simsek et al. (2013)** who concluded that, P wave dispersion and QTcD are increased in psoriasis patients and correlated with disease duration. In addition PWD correlated with diastolic function parameters of IVRT and DT. Our findings suggest that increased PWD and QTd are potentially useful, simple, and noninvasive methods for the early detection of subclinical cardiac involvement in patients with especially long-lasting psoriasis. They suggest that long-lasting psoriasis patients may be considered for referral for cardiovascular evaluation.

In short, results of the present study found an association between MPO and psoriasis severity and duration of disease in children; and it can be said that MPO played a role in the pathogenesis of the disease. However, there was no association between MPO and risk factors of CVD in those children denting that, MPO do not play a role in development of CVD in children with psoriasis. Larger and longer-term studies

are necessary to evaluate clinical implications of our finding.

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5/28/2015