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Serum paraoxonase-1 activity in Egyptian premenopausal women with metabolic syndrome and its relation with recurrent pre-eclampsia risk

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ABSTRACT

Background: Association of paraoxonase-1 (PON-1) with the metabolic syndrome (MS) and recurrent pre-eclampsia has not been previously investigated among Egyptian premenopausal women. Pre-eclampsia is a multisystem disorder and its etiopathogenesis has not yet been fully understood. **Aim**: The aim of the study is to investigate serum PON-1 activity in Egyptian women with MS and assess its potential link with the incidence of recurrent pre-eclampsia. **Method**: The study group consisted of 60 premenopausal women with MS and 60 healthy controls. In the MS group, 26 patients had past history of recurrent pre-eclampsia. The enzymatic activity of serum PON-1 was measured by spectrophotometer. Serum lipids were measured by enzymatic colorimetric methods using a Hitachi auto-analyzer. **Results**: MS cases with and without recurrent pre-eclampsia showed significantly reduced PON-1 activity compared to healthy controls. Significant negative correlations were observed between PON-1 levels and BMI, SBP, DBP, serum total cholesterol, TG and LDL-C and positive correlation with HDL–C in MS cases either with or without recurrent pre-eclampsia. In addition, MS cases with history of recurrent pre-eclampsia showed significantly lower levels of PON-1 than those without. **Conclusions**: Serum PON-1 is significantly reduced in women with MS and might alter their lipid profile. Low PON-1 levels could contribute to the great risk of recurrent pre-eclampsia in MS women.

INTRODUCTION

Paraoxonase-1 (PON-1) is a high-density lipoprotein (HDL) associated esterase enzyme that has a well-established antioxidant and anti-inflammatory properties (Kunutsor *et al*., 2016). It protects both low-density lipoprotein cholesterol (LDL-C) and HDL cholesterol (HDL-C) against oxidative damage (Manolescu *et al*., 2015). The antioxidant and anti-inflammatory properties of PON-1 have been found to be associated with CVD risk; although this association is partially dependent on HDL-C levels (Eren *et al*., 2013). There is a variation among individuals and populations in the PON-1 activity (Browne *et al*., 2007).

A reduced PON-1 activity has been reported in clinical conditions accompanied by low HDL-C such as the metabolic syndrome (MS) and Type 2 diabetes mellitus (DM) (Mackness *et al*., 1991). Nevertheless, there is a lacking in the current knowledge concerning the mechanisms responsible for regulating PON-1 activity.

Metabolic syndrome (MS) is a prevalent and complicated disorder that characterized by insulin resistance, hyperglycemia, abdominal obesity, arterial hypertension, atherogenic dyslipidemia, a prothrombotic state, and a proinflammatory state. These risk factors lead to the development of type 2 DM and cardiovascular (CV) diseases. Lots of studies observed low levels of PON-1 activity in patients with DM (Flekač *et al*., 2008). Several studies have examined the PON-1 activity in metabolic syndrome and insulin resistance patients, however, results from non-diabetic subjects showed contradictions. In non-diabetic Swiss population, an association has been observed between the significantly lower

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serum PON-1 concentrations and metabolic syndrome (Garin *et al*., 2005). However, A study on non-diabetic Turkish individuals showed no differences in the PON-1 activity between metabolic and non-metabolic cases (Tabur *et al*., 2010). In non-diabetic Japanese subjects, Yamada *et al.* (2001) have observed a positive correlation between the Homeostasis Model Assessment (HOMA) index and HDL-corrected PON-1 activity. In patients with MS, the role of PON-1 against peroxidation of LDL-C may be substantial. Decreased activity of PON-1 might play a role in the pathogenesis of atherosclerosis via rising the susceptibility to lipid peroxidation in patients with MS.

Pre-eclampsia is a disorder characterized by hypertension and proteinuria and causes maternal and perinatal mortality (Roberts and Cooper, 2001), though its etiopathogenesis has not yet been fully understood. In pre-eclampsia, a disturbance in the physiological remodeling of the uterine spiral arteries into dilated uteroplacental vessels observed in normal pregnancies is evident (Craven *et al*., 1998). A disagreement between studies that investigated the serum PON-1 activities in pre-eclamptic subjects has been observed. Some studies reported significantly higher paraoxonase activity in pre-eclamptic pregnant women compared to controls (Yaghmaei *et al*., 2011). Higher paraoxonase activity in severe compared to mild pre-eclampsia has also been observed. Other studies, however, found lower PON-1 in pre-eclamptic pregnant women compared to the controls (Genc *et al*., 2011). On the other hand, other authors have reported no differences in the paraoxonase activity between normal, mild and severe pre-eclamptic pregnant women (Sarandöl *et al*., 2004). As PON-1enzyme plays an antioxidant role in protecting LDL from oxidation, it has been assumed that PON-1 enzyme might be associated with diseases that oxidative stress implicated in their pathogenesis. However, the association between serum PON-1 activity and MS with recurrent pre-eclampsia has not yet been elucidated.

So, the aim of this study was to measure serum PON-1 activity in women with MS and to investigate its relation with recurrent pre-eclampsia risk.

MATERIALS AND METHODS

Subjects

Sixty premenopausal women with MS and 60 healthy (31.5 ± 2.9 yrs.) women were included in the study. In the MS group, 26 patients had past history of recurrent pre-eclampsia.

Inclusion criteria for subjects were women < 40 years old with MS.

Exclusion criteria for subjects were women with endocrine, metabolic kidney disease, or medical problems other than MS.

Subjects without and with MS, defined according to the revised NCEP-ATP III criteria (Grundy *et al*., 2005). Further inclusion criteria were cases with past history of pre-eclampsia in previous pregnancy/pregnancies. The subjects were patients in the obesity clinic at the National Research Centre. Control subjects included in the study were age match healthy women with normotensive and uncomplicated pregnancies history. Pre-eclampsia was defined as an increase in blood pressure to at least 140/90 mmHg after the 20 week of gestation, an increase in diastolic blood pressure (DBP) of at least 15 mmHg from the level measured before the 20 week, an increase in systolic blood pressure (SBP) of at least 30 mmHg from the level measured before the 20 week, combined with proteinuria (at least 0.3g per 24 hours) (Program, 2000).

The diagnosis of pre-eclampsia was established in accordance with the definition of the American College of Obstetricians and Gynecologist (Canadian Task Force on the Periodic Health Examination, 1994; Diaz *et al*., 2006).

Plasma lipids levels in control and MS subjects are shown in Table 1. Controls and patients were not taking lipid-lowering drugs, angiotensin-converting enzyme inhibitors, antioxidants, or other medication that could affect lipid metabolism. Smokers were excluded from the study, because cigarette smoke has been shown to inhibit paraoxonase activity. Furthermore, subjects with a current or recent illness were excluded from the study.

Informed consent was obtained from each participating subject. This research has been approved by the Ethical Committee of National Research Centre, Egypt (number = 16361), in accordance with the World Medical Association's Declaration of Helsinki.

Methods

Ascertainment of incident hypertension

Incident hypertension was defined as systolic blood pressure (SBP) of ≥140 mmHg, a diastolic BP of ≥90 mmHg, or the use of antihypertensive medication, in accordance with recommendations from the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Expert Panel on Detection, 2001). We used this definition to ensure consistency of hypertension in previous medical reports. Data on the use of antihypertensive medications were ascertained by questionnaires at each examination.

Anthropometric measurements

Anthropometric variables included body weight and height. Height was measured with the patients standing with their backs leaning against the stadiometer of the same scale. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Anthropometric measurements were obtained according to standardized equipment and following the recommendations of the International Biological Program (Tanner *et al*., 1969). Obese subjects had BMI greater than or equal to 30 kg/m^2 and overweight subjects had BMI ranged 25-29.9 kg/m^2.

Laboratory tests

Venous blood samples were collected by direct venipuncture after an overnight fast (minimum 12 h).

Measurement of paraoxonase activity

The enzymatic activity of serum PON-1 was measured by spectrophotometer (Sigma Chemical Co., St. Louis, MO). Paraoxonase activity was expressed as U/l serum (Haagen and Brock, 1992). The inter-assay CV was 8%.

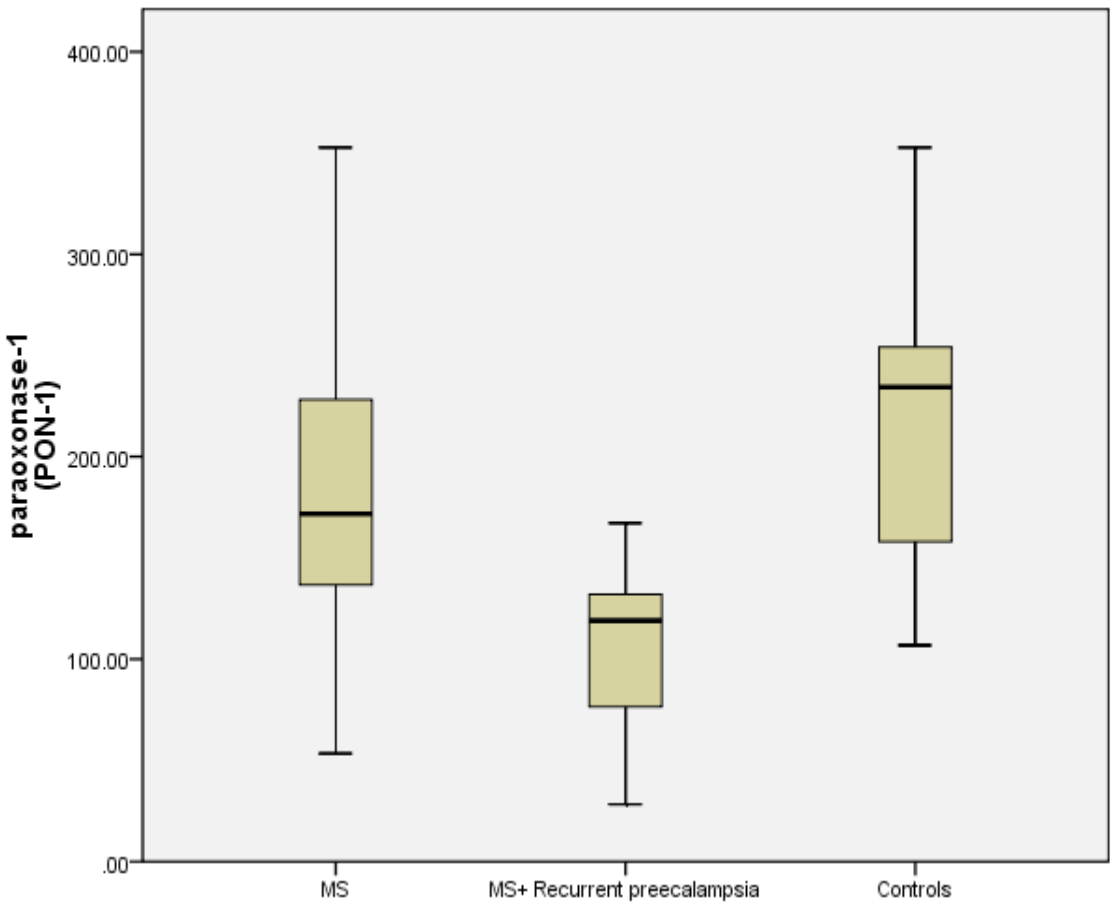

Fig. 1: Serum paraoxonase 1 activity in the MS group, MS + recurrent pree-clampsia subgroup and controls.

Blood lipids and HOMA-IR measurements

Fasting plasma glucose and serum lipids (total cholesterol, high-density lipoprotein cholesterol (HDL-C) triglycerides (TG)) were measured by enzymatic colorimetric methods using a Hitachi auto-analyzer 704 (Roche Diagnostics. Switzerland) (Hirschler *et al*., 2010). Low density lipoprotein cholesterol (LDL-C) was calculated according to certain equation (LDL-C = Total cholesterol – Triglycerides/5 + HDL-C). Serum insulin concentration was analyzed by chemiluminescent immunoassay (Immulite 2000, Siemens, Germany). Insulin resistance was determined by the Homeostasis Model Insulin Resistance (HOMA-IR) which is calculated as the product of the fasting plasma insulin level (IU/mL) and the fasting plasma glucose level (mmol/L), divided by 22.5 (Matthews *et al*., 1985). Each subject had a clinical history taken and physical examination was also performed.

Statistical analysis

Data were statistically analyzed using Statistical Package for the Social Sciences version 16 software (SPSS Inc.; Chicago, IL, USA). Parameters were expressed as mean ± SD. The correlations of variables were assessed in each group using Pearson Correlation Analysis. ANOVA tests were performed comparing 3 groups, and 2 groups were compared using independent T-tests. To determine significant differences between groups, the Post-Hoc test with Bonferroni correction was used. Pearson correlation test was used to study the relation between serum paraoxonase, lipid and metabolic parameters. For comparing clinical and laboratory results between the groups, we used Student t-tests or Mann-Whitney U test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Table 1 shows clinical and metabolic data of MS cases with and without recurrent pre-eclampsia and control group. Mean ages of the three groups were similar. In MS group FBG, BMI, TC, TG, SBP, DBP, and HOMA-IR levels were significantly higher than controls while PON-1 and HDL-C were significantly lower. Similar results were observed in MS with recurrent pre-eclampsia subgroup as compared to the control group. Moreover, MS cases with recurrent pre-eclampsia showed significant higher BMI and HOMA-IR and lower PON-1 compared to those without.

Analyses of the correlation between lipid and metabolic parameters with enzymatic activities of PON-1 are shown in Table 2. Correlation analyses showed significant negative correlation between PON-1 and BMI, total cholesterol, LDL-C, triglycerides and HOMA-IR and significant positive correlation with HDL-C in MS cases. In addition, a similar pattern of correlations between the enzyme activity and metabolic and biochemical parameters was

observed in women that had recurrent pre-eclampsia and MS.

Table 1: Clinical characteristics, activity of paraoxonase (PON-1), metabolic and lipid parameters in serum of women with MS, recurrent pre-eclampsia and controls.

Variables	Group	Mean ± SD
Age (years)	MS (n = 34)	31.2 ± 3.61
	MS + Recurrent pre-eclampsia (n = 26)	33.4 ± 3.22
	Controls (n = 60)	32.5 ± 4.2
PON-1	MS (n = 34)	180.98 ± 22.54[a]
	MS + Recurrent pre-eclampsia (n = 26)	106.33 ± 27.41[a b]
	Controls (n = 60)	222.47 ± 25.02
BMI (kg/m^2)	MS (n = 34)	28.61 ± 6.84[a]
	MS + Recurrent pre-eclampsia (n = 26)	34.22 ± 3.23[a b]
	Controls (n = 60)	23.23 ± 4.91
FPG (mg/dL)	MS (n = 34)	93.34 ± 23.70[a]
	MS + Recurrent pre-eclampsia (n = 26)	121.71 ± 23.83[a]
	Controls (n = 60)	85.71 ± 16.72
TC (mg/dL)	MS (n = 34)	188.82 ± 46.96
	MS + Recurrent pre-eclampsia (n = 26)	210.75 ± 34.14
	Controls (n = 60)	186.20 ± 30.773
TG (mg/dL)	MS (n = 34)	162.44 ± 31.66[a]
	MS + Recurrent pre-eclampsia (n = 26)	165.50 ± 32.75[a]
	Controls (n = 60)	86.67 ± 30.951
HDL-C (mg/dL)	MS (n = 34)	42.30 ± 11.68[a]
	MS + Recurrent pre-eclampsia (n = 26)	43.00 ± 7.07[a]
	Controls (n = 60)	55.33 ± 8.92
LDL-C (mg/dL)	MS (n = 34)	123.75 ± 30.556[a]
	MS + Recurrent pre-eclampsia (n = 26)	124.25 ± 29.88[a]
	Controls (n = 60)	127.47 ± 26.99
SBP (mmHg)	MS (n = 34)	127.05 ± 7.15[a]
	MS + Recurrent pre-eclampsia (n = 26)	128.50 ± 9.82[a]
	Controls (n = 60)	96.67 ± 6.14
DBP (mmHg)	MS (n = 34)	92.05 ± 8.490[a]
	MS + Recurrent pre-eclampsia (n = 26)	96.50 ± 7.07[a]
	Controls (n = 60)	70.42 ± 8.107
HOMA-IR	MS (n = 34)	2.68 ± .47[a]
	MS + Recurrent pre-eclampsia (n = 26)	3.55 ± .02[a b]
	Controls (n = 60)	1.46 ± .51

[a]$P < 0.001$ *vs*. control subject. [b]$P < 0.001$ *vs. MS.*

Figure 1 illustrates the level of PON-1 in the three groups. Box plot shows mean (SD) of MS, MS + recurrent pre-eclampsia subgroup and control group. Women with MS + recurrent pre-eclampsia had the lowest mean (106.33 ± 27.41) level of PON-1 compared to both control (222.47 ± 25.02) and MS cases without pre-eclampsia (180.98 ± 22.54). The lower boundary of the box is the 25th percentile and the upper boundary is the 75th percentile. The bold line inside the box represents the median. The largest and smallest observed values that are not extreme values are also shown.

Table 2: Correlation of enzymatic activity of PON-1 with metabolic and lipid parameters in women with MS and **MS + Recurrent** pre-eclampsia.

	PON-1			
	MS (n = 34)		MS + Recurrent pre-eclampsia (n = 26)	
	r	p	r	p
HOMA-IR	-.34	.01	-.35	.01
FBG (mg/dl)	-.38	.01	-.58	.001
TC (mg/dl)	-.39	.02	-.46	.001
TG (mg/dl)	-.32	.05	-.52	.005
HDL-C (mg/dl)	.32	.05	.35	.05
LDL-C (mg/dl)	-.30	.05	-.36	.01
SBP (mmHg)	-.36	.01	-.37	.01
DBP (mmHg)	-.31	.05	-.34	.01
BMI (kg/m^2)	-.29	.05	-.37	.01

HOMA-IR: homeostasis model assessment-insulin resistance; FBG: fasting glucose; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; r: Pearson product-moment correlation coefficient or Spearman's rank correlation coefficient as appropriate.

DISCUSSION

It is well known that obesity is associated with insulin resistance. It has been found that hyperinsulinaemia as a marker of insulin resistance increase the risk of mild pre-eclampsia. The complex connection between obesity, insulin resistance and pre-eclampsia is not yet completely understood. Weight loss in obese individuals has health benefits that could justify getting rid of extra weight before pregnancy (Bhattacharya *et al*., 2009). In our study, subjects with MS showed, as expected, significantly higher BMI, HOMA-IR, in addition to dyslipidemia and hypertension. MS cases with recurrent pre-eclampsia cases showed significantly higher BMI and HOMA-IR compared to MS and control groups.

In agreement with our results, a previous study found higher risk of recurrent pre-eclampsia (19.3%) among obese women compared to those with normal BMI (11.2%) (Mostello *et al*., 2008). Results of the present study showed significantly lower PON-1 and HDL-C in both MS and MS with recurrent pre-eclampsia subjects in comparison to the control group. Moreover, PON-1 activity was found to be significantly lower in MS cases with recurrent pre-eclampsia than those without pre-eclampsia. In aggrement with our results, Genc and colleagues (2011) reported low PON- activity in pre-eclampsia cases.

Some studies have reported a correlation between serum paraoxonase activity and several lipid and lipoprotein parameters such as triglycerides and HDL (Sözmen *et al*., 1999). We found similar correlations in the present study. Decreased PON-1 activity has been previously reported in MS cases compared to control, however, Tabur *et al.* (2010) showed that non-diabetic MS does not affect serum paraoxonase activity. Reduced serum PON-1

activity is likely to be found in clinical conditions accompanied by low HDL cholesterol such as MS and Type 2 diabetes mellitus (T2DM) (Garin, *et al.*, 2005). Furthermore, Women who suffered from Polycystic Ovarian Syndrome (PCOS) and obesity showed elevated insulin resistance and significantly lower PON-1 levels (Dursun *et al*., 2005). The protective role of Paraoxonase against LDL and HDL oxidation is probably related to its ability to hydrolyze some oxidized phospholipids (Watson *et al*., 1995). In the present study, significantly negative correlations have been found between the PON-1 activity and blood pressure in MS cases either with or without pre-eclampsia. According to an extensive prospective study, no association between serum PON-1 and the future risk of hypertension has been found (Kunutsor *et al*., 2017a). Although the same study has reported an independent and inverse association between HDL-C and incident hypertension. Other studies have also reported the inverse and independent association between the HDL-C and the risk of hypertension (Tohidi *et al*., 2012).

In the present study, PON-1 activity was positively correlated with HDL-C in both MS cases with or without pre-eclampsia. HDL has antithrombotic activities as it is able to sweep cholesterol out of the atheromatous arteries. PON-1 is an important constituent of HDL and it has antioxidant and anti-inflammatory properties and has its site of action on HDL (Dullaart *et al*., 2013). Furthermore, PON-1 has a protective role against atherosclerosis and cardiovascular disease (Sentí *et al*., 2003). Lots of evidence suggest that the antioxidant properties of HDL and its capacity in protecting LDL oxidation could be attributed to PON-1 activity. HDL-C is involved in the commonly used cardiovascular risk algorithms (Task *et al*., 2016) and it is a substantial risk factor for atherosclerotic cardiovascular disease (CVD).

The protective association between HDL-C and cardio-metabolic outcomes is evident, so, it was not expected to find no association between PON-1 and hypertension. However, it has also been shown that there is no association between PON-1 and type 2 diabetes although, the inverse independent association between HDL-C and type 2 diabetes is evident (Kunutsor *et al*., 2017b) indicting that the association is independent of and not modified by PON-1. So, apparently, there might be significant pathophysiologic variations between HDL-C and PON-1in the pathogenesis of these cardio-metabolic outcomes. It is possible that these results might reflect the different HDL subclasses or particle sizes, which apparently affect its protective ability against LDL oxidation. It has been suggested that lipids play a role in the development of hypertension, although the mechanisms of this process are not fully understood. In contrast to total cholesterol, LDL-C, triglycerides and apolipoprotein B which are linked to an increased risk of hypertension, HDL-C has a protective role (Halperin *et al*., 2006). The underlying mechanism of the associations between dyslipidemia and the incidence of hypertension might be through endothelial dysfunction. The precise mechanism affecting low PON-1 levels in MS is still not fully understood. Although a decline in the PON-1 activity has been reported in MS, PON-1 codon 192 genotype distribution was found to be similar in both MS cases and controls (Sentí *et al*., 2003). It has been demonstrated that lipid-lowering treatments improve PON-1 serum activity (Ribas *et al*., 2004).

In conclusion, our study showed that PON-1 serum activity was reduced in the MS group as well as in MS with recurrent pre-eclampsia subgroup as compared to controls. Therefore, it is important to measure the serum PON-1 activity in women with MS to improve the power of identifying cases at high risk of pregnancy complications and in interventions against metabolic-related disorders.

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