Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 396–400

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Association of myeloperoxidase with cardiovascular disease risk factors in prediabetic subjects

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ARTICLE INFO

Article history:
Received 5 September 2018
Accepted 10 October 2018

Keywords:
Prediabetes
Myeloperoxidase
Atherosclerosis
Cardiovascular disease

ABSTRACT

Introduction: Prediabetes is a chronic low-grade inflammatory disease and considered as a risk factor for the development of diabetes mellitus and cardiovascular disease. Myeloperoxidase (MPO) is a leukocyte-derived enzyme, linked to both oxidative stress and inflammation and has been proposed as a possible mediator of atherosclerosis, the major cause of cardiovascular disease. The objective of the present study was to evaluate the level of MPO in prediabetic subjects and correlate it with other cardiovascular disease risk factors.

Materials and methods: In this cross-sectional study, a total of 400 subjects were recruited. Of them, 200 were prediabetic subjects and 200 were age and gender-matched controls. For each subject, blood pressure, weight, height, waist circumference, hip circumference and lipid parameters were measured. In addition, MPO was determined.

Results: MPO was significantly increased in prediabetic subjects as compared to controls. In correlation analysis, MPO was found to be significantly and positively correlated with all the cardiovascular disease risk factors i.e. age, body mass index (BMI), waist-to-hip ratio (WHR), blood pressure [both systolic blood pressure (SBP) and diastolic blood pressure (DBP)], lipid parameters except high density lipoprotein (HDL) to which it was negatively correlated.

Conclusion: In conclusion, MPO is well correlated with cardiovascular disease risk factors in prediabetes. Hence, MPO could be used to detect cardiovascular risk among prediabetic subjects and also can be used as an early biomarker of oxidative stress and inflammation in prediabetes.

1. Introduction

The prevalence of diabetes is increasing rapidly all over the globe at an alarming rate [1]. Over the past 30 years, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle-aged people. It is important to note that the increase in the prevalence of diabetes mellitus is seen in all six inhabited continents of the globe [2]. According to the pathogenesis and natural history of diabetes, it has a prolonged prediabetic phase, which is considered to be a high-risk state for diabetes [3] and can be defined by glycemic levels that are higher than normal but below the diagnostic parameters required for a diagnosis of diabetes [4]. It is estimated that about 10% of the population have prediabetes, although only one third know it. The average risk of development of diabetes increases 0.7% per year in people with normal glucose levels, and 5–10% per year in prediabetic patients [5]. The prevalence of prediabetes is increasing worldwide and the International Diabetes Federation estimated that the worldwide prevalence of prediabetes was 318 million in the year 2015 and projected to rise to 482 million by the year 2040 [6]. In India, the prevalence of prediabetes was reported to be 10.3% in the year 2017 [7]. Prediabetic patients manifest all the cardiovascular disease risk factors such as dysglycemia, dyslipidemia, obesity, hypertension, physical inactivity, procoagulant state, insulin resistance, inflammation, oxidative stress and endothelial

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https://doi.org/10.1016/j.dsx.2018.10.016
1871-4021/

dysfunction and have a higher susceptibility for macrovascular disease development [8,9]. In the recent years, prediabetes has received increasing attention not only because it is an intermediate stage in the development of diabetes and cardiovascular diseases (CVDs) [10,11], but also because it is associated with increased risk of all-cause death and CVD mortality [12].

Chronic low-grade inflammation precedes the onset of diabetes and the degree of subclinical inflammation was reported to be similar in both prediabetes and individuals with diabetes [13,14]. Low-grade inflammation is one of the major underlying pathophysiologic mechanisms responsible for endothelial dysfunction and atherosclerotic plaque formation, processes which contribute to the development of cardiovascular disease (CVD) [15]. Several inflammatory markers have been associated with a greater likelihood of cardiovascular diseases. Of those, myeloperoxidase (MPO) is the most well known [16]. Myeloperoxidase (MPO), a product of systemic inflammation plays an important role both in the process of oxidative stress and inflammation and promotes oxidation of lipoproteins. MPO is a leukocyte-derived enzyme that catalyzes the formation of oxidative reactants and participates in innate immunity against infections [17]. However, MPO also plays an important role in the initiation and progression of acute and chronic inflammatory diseases, fundamentally cardiovascular diseases (CVD) [18].

As far as we know, no data have been reported regarding the relationship between MPO and cardiovascular disease risk factors among prediabetic subjects. Furthermore, we hypothesized that there might be a strong relationship between MPO and cardiovascular disease risk factors in prediabetes. Hence, we designed this study with the aim to evaluate the level of MPO in prediabetic subjects and correlate it with other cardiovascular disease risk factors.

2. Materials and methods

2.1. Study design and inclusion criteria

This cross-sectional study was conducted in the Department of Biochemistry, Gajra Raja Medical College, Gwalior, India. A total of 400 human subjects were included in the present study, out of which 200 were prediabetic subjects, aged between 20 and 55 years of either sex and rest 200 were age and gender-matched control subjects. The participants were selected from general population, and those who were at risk of developing diabetes (who had at least one of the main risk factors for diabetes-first degree relative with diabetes, BMI $\geq$25 kg/m^2, women who were diagnosed with gestational diabetes mellitus, women with polycystic ovary syndrome, persons who are physically inactive, and other clinical conditions associated with insulin resistance, for example, severe obesity, acanthosis nigricans, etc.) in Gwalior City through a predesigned screening questionnaire. The study was approved by the Ethics Committee of Gajra Raja Medical College, Gwalior, India (Ref. No: 286/Bio/MC/Ethical, Approval date: 3 March 2017), and all participants gave written and verbal informed consent consistent with the Helsinki declaration.

The prediabetic subjects were diagnosed on the basis of the American Diabetes Association (ADA) guidelines as:

a) Fasting plasma glucose level 100–125 mg/dL (Impaired fasting glucose, IFG) and
b) 2-h plasma glucose (after giving 75 gm of glucose) level 140–199 mg/dL (Impaired glucose tolerance, IGT) [19].

Those with a normal range of blood glucose level had been selected as the control group (Fasting plasma glucose (FPG) < 100 mg/dL, 2-h plasma glucose concentration after giving 75 gm of glucose <140 mg/dL).

2.2. Exclusion criteria

Subjects with type 2 diabetes mellitus, cardiovascular disease, renal disease, hepatic disease, pulmonary tuberculosis, acute or chronic inflammatory disease, gout and arthritis, prolonged illness, subjects not willing to give consent or refuse to participate in the study, and patients receiving medicines known to alter glucose and lipid metabolism were excluded from the present study. Patients with triglyceride levels of 400 mg/dL and above were also excluded from the study.

2.3. Anthropometric measurements

Both weight and height were measured in light clothes and without shoes, using the standard apparatus. The weight was measured using calibrated electronic weighing scales prior to eating in the morning and height was measured to the nearest centimeter using a portable stadiometer. Body mass index (BMI) of the participants was calculated using a standard formula, BMI=-Weight (Kg)/[Height (m)]^2. Waist circumference (WC) was measured using an anthropometric tape at a level on the skin midway between the mean point of iliac peak and the inferior border of the last rib at the level of the umbilicus while in a standing position at the end of gentle expiration. Hip circumference (HC) was measured over the widest part of the gluteal region at the level of pubic tubercle in standing position. Waist-to-hip ratio (WHR) was obtained by waist circumference (cm) divided by hip circumference (cm).

2.4. Blood pressure measurements

The systolic and diastolic blood pressures were taken after 10 min of resting by using a standardized mercury sphygmomanometer using standard recommended procedures.

2.5. Biochemical measurements

Venous blood samples were obtained from all participants under all aseptic precautions after at least 10–12 h of overnight fasting for biochemical investigation. After that, 75 gm of glucose was given orally to each participant and plasma glucose concentrations were measured at 120 min during an oral glucose tolerance test (OGTT). The biochemical parameters namely glucose, total cholesterol, triglyceride, and HDL were analyzed on Mindray BS-400 chemistry analyzer (Mindray Medical International Ltd., Shenzhen, China) using commercially available kits from ERBA Diagnostics Mannheim, Germany. LDL-Cholesterol and VLDL-Cholesterol were calculated using the Friedewald equation [20]. MPO in serum was estimated by ELISA using a commercially available kit from R & D Systems, Inc, USA (Catalog Number: DMYE00B).

2.6. Statistical analysis

All the data were presented as mean $\pm$ standard deviation. Statistical Package for Social Science version 20 (IBM, SPSS Statistics 20, Armonk, NY, USA) was used for data analysis. Shapiro-Wilk test was used to check the normal distribution of data. Student independent sample *t*-test was used for intergroup comparisons of normally distributed parameters whereas the Mann-Whitney *U* test was used for the intergroup comparisons of skewed data. Chi-square test was used for categorical data. Pearson's correlation was used to find the possible relationship between studied parameters. A p value of less than 0.05 was considered to be statistically significant.

3. Results

Table 1 shows the sociodemographic characteristics of the studied subjects. Subjects with both the groups were age and gender matched since there was no difference in terms of age and gender between prediabetic and control subjects. Subjects with prediabetes had significantly increased mean BMI, WC, HC, and WHR than the control subjects (29.08 ± 1.66 kg/m^2 vs. 23.42 ± 0.94 kg/m^2, $p < 0.001$; 92.02 ± 3.91 cm vs. 82.51 ± 2.82 cm, $p < 0.001$; 95.99 ± 2.61 cm vs. 95.42 ± 2.42 cm, $p < 0.05$ and 0.96 ± 0.03 vs. 0.86 ± 0.03, $p < 0.001$, respectively), indicating that prediabetic subjects had higher rate of general obesity (based on BMI) and central obesity (based on WHR). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly increased in prediabetic subjects as compared to controls (127.00 ± 5.66 mmHg vs. 116.30 ± 3.31 mmHg, $p < 0.001$ and 81.87 ± 3.63 mmHg vs. 77.48 ± 3.36 mmHg, $p < 0.001$, respectively). Table 2 shows the biochemical characteristics of the studied subjects. The total cholesterol, triglyceride, LDL-C and VLDL-C were significantly increased in prediabetic subjects as compared to controls (190.67 ± 18.44 mg/dL vs.180.19 ± 14.33 mg/dL, $p < 0.001$; 148.19 ± 18.80 mg/dL vs. 120.70 ± 19.84 mg/dL, $p < 0.001$; 128.22 ± 18.60 mg/dL vs. 113.20 ± 14.47 mg/dL, $p < 0.001$ and 29.64 ± 3.76 mg/dL vs. 24.14 ± 3.97 mg/dL, $p < 0.001$, respectively). Patients with prediabetes had significantly lowered HDL values compared with control subjects (32.81 ± 2.79 mg/dL vs. 42.86 ± 3.40 mg/dL, $p < 0.001$). Prediabetic subjects had significantly increased concentration of MPO as compared to controls (90.34 ± 8.42 ng/mL vs. 58.45 ± 7.20 ng/mL, $p < 0.001$). Table 3 shows the correlation of MPO with cardiovascular disease risk factors in prediabetic subjects. MPO was significantly and positively correlated with all the cardiovascular disease risk factors, i.e., age ($r = 0.282$; $p < 0.01$), BMI ($r = 0.418$; $p < 0.01$), WHR ($r = 0.340$; $p < 0.01$), SBP ($r = 0.398$; $p < 0.01$), DBP ($r = 0.327$; $p < 0.01$), FPG ($r = 0.618$; $p < 0.01$), 2-h PG ($r = 0.402$; $p < 0.01$), TC ($r = 0.358$; $p < 0.01$), TG ($r = 0.412$; $p < 0.01$), LDL ($r = 0.319$; $p < 0.01$), and VLDL ($r = 0.412$; $p < 0.01$), but not with HDL ($r = -0.317$; $p < 0.01$), which was negatively correlated in prediabetic subjects.

4. Discussion

This was the first cross-sectional study where the relationship between MPO and cardiovascular disease risk factors has been evaluated among Indian prediabetic subjects. The main findings of this study were that the level of MPO was increased in prediabetic subjects and this enzyme was positively correlated with cardiovascular risk factors namely glucose, BMI, WHR, SBP, DBP, TC, TG, LDL and VLDL except for HDL to which it was negatively correlated.

Prediabetes is the intermediate state of abnormal glucose regulation that lies between normal blood glucose levels and type 2 diabetes mellitus and has been considered as a risk factor for diabetes mellitus and atherosclerotic cardiovascular disease (CVD) [21]. The main hypothesis for the origin of atherosclerosis considers it to be an inflammatory process that occurs in different forms, leading to vascular endothelium injury. Chronic inflammatory processes favor clinical progression of atheroma plaques, which may suffer rupture and provoke thrombus formation and complications associated with atherosclerosis [22,23].

Myeloperoxidase is an oxidative stress and inflammatory factors that play important role in promotion and propagation of atherosclerosis [17]. Our study showed a statistically significant increase in the level of MPO in prediabetic subjects as compared to control subjects, which is in line with a study done by Agarwal et al. [9]. A similar finding has been reported by Shetty et al. [24] in patients of type 2 diabetes mellitus. Moreover, MPO was significantly and positively correlated with blood glucose in prediabetic subjects. The result of the present study indicates that oxidative stress, low-grade inflammation, and endothelial dysfunction appear even before the onset of full-blown diabetes, which may lead to the initiation and progression of cardiovascular disease. Hyperglycemia and diabetes mellitus have been shown to be associated with activation of leukocyte counts [25,26]. As prediabetes is characterized by hyperglycemia, the present study clearly supports this concept showing that circulatory MPO predominantly derived from leukocytes are higher in prediabetes. In addition, elevated serum MPO levels have been associated with increased CVD risk in apparently healthy individuals [27]. MPO has proved to be an active mediator of endothelial dysfunction in cell culture, animal models [28], and adult humans [29]. Moreover, high glucose stimulates the

Table 1
Sociodemographic characteristics of the control and prediabetic subjects.

Variables	Control Subjects (n = 200)	Prediabetic Subjects (n = 200)
Age (years)	39.07 ± 7.60	39.90 ± 8.84^{NS}
Sex (M/F)	112/88	$106/94^{NS}$
BMI (kg/m2)	23.42 ± 0.94	$29.08 \pm 1.66^{**}$
WC (cm)	82.51 ± 2.82	$92.02 \pm 3.91^{**}$
HC (cm)	95.42 ± 2.42	$95.99 \pm 2.61^{*}$
WHR	0.86 ± 0.03	$0.96 \pm 0.03^{**}$
SBP (mmHg)	116.30 ± 3.31	$127.00 \pm 5.66^{**}$
DBP (mmHg)	77.48 ± 3.36	$81.87 \pm 3.63^{**}$

BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist to hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ^{NS}Not significant; *Significant at $p < 0.05$; **Significant at $p < 0.001$.

Table 2
Biochemical characteristics of the control and prediabetic subjects.

Variables	Control Subjects (n = 200)	Prediabetic Subjects (n = 200)
FPG (mg/dL)	90.19 ± 3.83	$116.13 \pm 3.62^{**}$
2-h PG (mg/dL)	123.65 ± 6.20	$150.13 \pm 4.16^{**}$
TC (mg/dL)	180.19 ± 14.33	$190.67 \pm 18.44^{**}$
TG (mg/dL)	120.70 ± 19.84	$148.19 \pm 18.80^{**}$
HDL (mg/dL)	42.86 ± 3.40	$32.81 \pm 2.79^{**}$
LDL (mg/dL)	113.20 ± 14.47	$128.22 \pm 18.60^{**}$
VLDL (mg/dL)	24.14 ± 3.97	$29.64 \pm 3.76^{**}$
MPO (ng/mL)	58.45 ± 7.20	$90.34 \pm 8.42^{**}$

FPG: Fasting plasma glucose; 2-h PG: 2-h post glucose; TC: Total cholesterol; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; MPO: Myeloperoxidase; **Significant at $p < 0.001$.

Table 3
Shows the correlation of MPO with cardiovascular disease risk factors in prediabetic subjects.

Variables	MPO	
	r-value	p-value
Age	0.282	$p < 0.01$
BMI	0.418	$p < 0.01$
WHR	0.340	$p < 0.01$
SBP	0.398	$p < 0.01$
DBP	0.327	$p < 0.01$
FPG	0.618	$p < 0.01$
2-h PG	0.402	$p < 0.01$
TC	0.358	$p < 0.01$
HDL	−0.317	$p < 0.01$
TG	0.412	$p < 0.01$
LDL	0.319	$p < 0.01$
VLDL	0.412	$p < 0.01$

BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; 2-h PG: 2-h plasma glucose; TC: Total cholesterol; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; MPO: Myeloperoxidase.

production of hydrogen peroxide (H_2O_2), and MPO can use H_2O_2 as a physiological substrate to form hypochlorous acid, resulting in increasing MPO activity [30]. Fu et al. [31] reported that hypochlorous acid production by MPO might represent a physiological mechanism that links degradation of matrix proteins by metalloproteinases. Several mechanisms have been described by which MPO can promote atherogenesis. First, MPO activity leads to oxidation and carbamylation of LDL-C, thus converting it into more atherogenic form [32,33]. Second, MPO generated products promote the impairment of the ability of apolipoprotein A1 (apoA-1) via its site-specific modification and dysfunction of HDL, which result in the reduction of cholesterol efflux, and the increase of lipid accumulation and foam cell formation [34,35]. Third, MPO catalytically consumes endothelium-derived nitric oxide, thereby reducing nitric oxide bioavailability and impairing its vasodilatory and anti-inflammatory functions, leading to plaque formation and endothelial dysfunction [28,36]. Finally, MPO has been shown to activate metalloproteinases and promote destabilization and rupture of the atherosclerotic plaque surface [31].

Patients in the prediabetes group showed significantly increased BMI and WHR, which are considered as indicators of general obesity and central obesity respectively. These findings are in agreement with the results of Agarwal et al. [9] and Ferrannini et al. [37], who reported that prediabetic subjects have increased BMI, WC and increased WHR compared to controls. Similarly, in a large cohort prospective study of men, Wang et al. [38] found that both BMI (indicator of general obesity) and WC (indicator of central obesity) predict the risk of type 2 diabetes mellitus. Moreover, MPO was strongly associated with BMI and WHR, indicating that obesity might create the environment of oxidative stress and inflammation which further predisposes prediabetic subjects to an increased risk for CVD.

Similar to the findings of Calanna et al. [39] and Wang et al. [40], we also found significantly increased blood pressure (both SBP and DBP) in prediabetic subjects as compared to controls. Pearson's correlation analysis revealed a statistically significant positive correlation between blood pressure and MPO in prediabetic subjects. Van der Zwan et al. [41] also found a stronger association between MPO level and blood pressure at high glucose concentration. During high blood pressure, there occurs increased release of inflammatory cytokines such as TNF-alpha and IL-8 and the activation of renin-angiotensin system, which could lead to neutrophil activation and respiratory burst [42,43], that might promote the release of MPO from neutrophils and resulted in increased circulatory MPO which further exacerbate the damage of vascular endothelial cells leading to increased risk for CVD in prediabetic subjects.

Dyslipidemia is also considered to play a major role in the pathophysiology of atherosclerosis and is associated with increased risk for the development of CVD [44]. In our study, we found significantly increased levels of TC, TG, LDL-C, and VLDL-C in prediabetic subjects as compared to controls except for HDL-C, which was significantly decreased. This dyslipidemic pattern in prediabetes is very much similar to the findings of previous studies [45–47]. This dyslipidemic pattern observed in prediabetic subjects can be attributed to the elevated free fatty acid levels as a consequence of resistance to the action of insulin on adipocytes [48]. In turn, these free fatty acids can stimulate hepatic triglyceride, VLDL production and reduced levels of HDL-C [49,50]. In addition, MPO is positively correlated with lipid parameters viz. TC, TG, LDL and VLDL except for HDL to which it was negatively correlated. This indicates that dyslipidemia might induce oxidative stress and creates an environment of inflammation that put prediabetic subjects at an increased risk for CVD. Apart from reducing blood cholesterol level, HDL-C has also got antioxidant and anti-inflammatory effects. In addition, HDL-C potently reduces neutrophil activation [51]. As HDL-C was negatively correlated with MPO concentration in prediabetic subjects, the neutrophils activity and release of MPO were increased with the reduction of HDL-C, resulting in increased MPO level in circulation.

The advantage of this study is that the subjects were selected on the basis of both fasting plasma glucose and 2-h plasma glucose (after giving 75 g of glucose). In addition, our study was carried out in a large sample size and was adequately powered since the significance of results was high. Despite advantages, our study has major limitations because of the cross-sectional nature of the data which limits the inferences about causal relationships.

5. Conclusion

In conclusion, subjects with prediabetes had increased MPO concentration, increased BMI and WHR, increased blood pressure and dyslipidemia, which indicates biochemical changes of atherosclerosis start even before the onset of diabetes mellitus. As obesity, hypertension, dyslipidemia, oxidative stress and inflammation are important cardiovascular risk factors in prediabetes, these factors should be assessed and treated in order to mitigate the risk for CVD. In addition, MPO is well correlated with cardiovascular disease risk factors in prediabetes. Hence, MPO could be used to detect cardiovascular risk among prediabetic subjects and also can be used as an early biomarker of oxidative stress and inflammation in prediabetes.

Funding

The authors received no financial support for the research.

Ethical approval

The study was approved by the Ethics Committee of Gajra Raja Medical College, Gwalior, India (Ref. No: 286/Bio/MC/Ethical, Approval date: 3 March 2017).

Conflicts of interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all the participants included in the study.

Acknowledgments

We wish to express our gratitude to all the volunteers who made this study possible. Special thanks to all the Ph.D. scholars and technical staffs of the Department of Biochemistry, Gajra Raja Medical College, Gwalior for their help during the research.

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