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Comparison of two consecutive fat-rich and carbohydrate-rich meals on postprandial myeloperoxidase response in women with and without type 2 diabetes mellitus

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Abstract

Patients with type 2 diabetes mellitus (DM2) have an increased risk of cardiovascular disease (CVD). Myeloperoxidase (MPO), expressed in leukocytes and released upon activation, is associated with CVD and endothelial dysfunction. Postprandial leukocyte recruitment and activation with subsequent MPO release may contribute to atherosclerosis and CVD. We hypothesized that MPO may increase in the postprandial state because of postprandial leukocyte recruitment and/or activation, especially in subjects with DM2. One hundred postmenopausal women, aged 50 to 65 years (66 with normal glucose metabolism [NGM] and 34 with DM2), received 2 consecutive fat-rich meals and 2 consecutive carbohydrate-rich meals on separate occasions. Blood samples were taken before ($t = 0$) and at 2, 4, and 8 hours after breakfast; lunch was given at $t = 4$. Plasma MPO concentration was measured by sandwich enzyme-linked immunosorbent assay. The number of leukocytes in fasting blood samples was higher in DM2 compared with NGM (6.1 ± 1.4 and $5.4 \pm 1.2 \times 10^9$/L, respectively; $P < .05$). Baseline MPO concentration did not significantly differ between NGM and DM2 (51.4 ± 12.9 and 54.5 ± 18.4 μg/L, respectively; $P = .39$). Baseline MPO was positively associated with leukocytes ($r = 0.20$, $P < .05$) and inversely associated with high-density lipoprotein cholesterol ($r = -0.22$, $P < .05$). Leukocytes increased from 5.0 ± 1.5 to $6.1 \pm 1.5 \times 10^9$/L and from 5.8 ± 1.4 to $6.6 \pm 1.4 \times 10^9$/L in NGM and DM2, respectively (both $P < .01$), after the fat-rich meals. In contrast to our hypothesized increase in MPO, we found a significant decrease in MPO in NGM (both meal types) and DM2 (fat-rich meals only). Our findings provide no support to our initial hypothesis that meal-induced release of MPO might be a mechanism that contributes to CVD risk.

1. Introduction

Patients with type 2 diabetes mellitus (DM2) have an increased risk of cardiovascular disease (CVD) [1-3]. In women, as compared with men, the relative risk of CVD conferred by DM2 is even higher, especially in postmenopausal women [4]. Evidence has been accumulating that chronic low-grade inflammation may be an important factor in the pathogenesis of atherosclerosis and CVD [5,6]. The number of white blood cells, especially polymorphonuclear neutrophils, is associated with future CVD events [7,8]. However, the role of leukocytes in the pathogenesis of CVD has not yet been fully elucidated. It has been demonstrated that the number of leukocytes was increased between 1 and 6 hours after a fat challenge [9]. Postprandial recruitment and activation of these cells have been suggested to contribute to endothelial dysfunction [10], which is an early event in the atherosclerotic process. Because postprandial responses after a fat-rich mixed meal may be more pronounced and prolonged in subjects with DM2 than in healthy controls [11], this may result in a

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higher postprandial leukocyte recruitment in these patients. This may be even more the case in postmenopausal women, who have higher postprandial triglyceride responses compared with premenopausal women [12].

Myeloperoxidase (MPO, EC no. 1.11.1.7) is a heme protein that is abundantly expressed in leukocytes and released upon activation into phagocytic vacuoles and in the extracellular space [13,14]. Several in vitro and in vivo studies have shown that MPO interacts with the vessel wall by various mechanisms, including binding and transcytosis through endothelial cells, and leads to hypochlorous acid generation, nitric oxide oxidation, and tyrosine nitration [15]. Myeloperoxidase has been associated with coronary artery disease [16], recurrent coronary events [17], heart failure [18], and endothelial dysfunction [19].

Postprandial leukocyte recruitment and activation with subsequent MPO activation may thus contribute to atherosclerosis and CVD, especially in patients with DM2 because of the prolonged and exaggerated dysmetabolic state. Based on these observations, we hypothesized that, in particular in subjects with DM2, MPO would increase in the postprandial state because of postprandial leukocyte recruitment and/or activation. Therefore, we assessed the postprandial MPO response after 2 consecutive fat-rich or carbohydrate-rich meals in women with DM2 and in women with normal glucose metabolism (NGM).

2. Materials and methods

2.1. Subjects and study design

The women included in the present study were part of a cross-sectional study to assess the effect and relative contributions of 2 consecutive fat-rich and carbohydrate-rich meals on markers of CVD risk in postmenopausal women with NGM (n = 76) and DM2 (n = 79). Women with DM2 (n = 522), recruited from the registry of the Diabetes Care System in the city of Hoorn, the Netherlands, and women who were randomly selected from the municipal registry of Hoorn (n = 541), aged 50 to 65 years at the beginning of the study, were invited to participate in the study. Of these 1063 women, 431 women were complete nonresponders, 258 women were not willing to participate, and 219 women did not meet the inclusion criteria, yielding 155 eligible participants. Inclusion criteria were postmenopausal status (no menses in the last 12 months), nonsmoking, no untreated endocrine disorder other than DM2, no use of short-acting insulin analogues, no use of peroxisome proliferator–activated receptor α and γ agonists, no use of oral corticosteroids, no use of hormone replacement therapy, no use of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins) (for NGM only), glycated hemoglobin (HbA_{1c}) <9.0%, fasting cholesterol <8.0 mmol/L, fasting triglycerides <4.0 mmol/L, systolic blood pressure <190 mm Hg, and no liver impairment or renal impairment. Women who were selected from the municipal registry underwent a 75-g oral glucose tolerance test to verify their glucose tolerance status (fasting glucose <6.1 mmol/L and 2-hour postload glucose <7.8 mmol/L). In addition to the above-mentioned inclusion criteria of the main study protocol, for the present analyses, we chose not to include DM2 women using statins (n = 38) because statins have been shown to downregulate MPO gene expression [20,21]. Thus, for the present study, 41 women with DM2 and 76 women with NGM were included. The protocol consisted of 3 separate visits, that is, a screening visit and 2 visits for the test meals. Postprandial meal responses were examined after the consumption of 2 consecutive standardized test meals (breakfast and lunch; fat-rich meals [3349 kJ; 50 g fat, 56 g carbohydrates, and 28 g proteins] and carbohydrate-rich meals [3261 kJ; 4 g fat, 162 g carbohydrates, and 22 g proteins]) on 2 separate occasions and in random order. Blood samples were taken before and at t = 2, 4, and 8 hours after breakfast for measurement of glucose, triglycerides, and MPO. Lunch was given 4 hours after breakfast (t = 4). Apart from the test meals and water (ad libitum), participants were not allowed to eat. In addition, physical activity was limited during the day. All participants gave informed consent, and the study protocol was approved by the ethics committee of the VU University Medical Center in Amsterdam.

2.2. Measurements

At the screening visit, blood pressure was measured at the left arm 3 times with 5-minute intervals with an oscillometric blood pressure measuring device (Collin Press-mate BP-8800; Colin, Komaki City, Japan) after a 15-minute supine rest. Waist circumference was measured twice at the level midway between the lowest rib margin and the iliac crest. Medical history was assessed by a questionnaire [22].

2.3. Laboratory analyses

Myeloperoxidase was determined in duplicate by a sandwich enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden) in EDTA plasma using a CODA Automated EIA Analyzer (Biorad, San Francisco, CA). The concentration of MPO was measured in baseline samples and in samples that were taken at 2, 4, and 8 hours after breakfast. The intraassay and interassay coefficients of variation were 3.3% and 5.0%, respectively. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose were measured by enzymatic colorimetric assays (Roche, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald-formula [23]. Glycated hemoglobin was measured with cation exchange chromatography (Menarini Diagnostics, Florence, Italy). Leukocytes were measured at baseline in all subjects and at 8 hours after breakfast in a subsample (n = 43; 29 NGM and 14 DM2) to determine the postprandial leukocyte response.

3. Statistical analysis

Analyses were performed in SPSS for Windows 11.0.1 (SPSS, Chicago, IL). Data are presented as mean values (standard deviation) or, in case of skewed distribution, as median values (interquartile range). Differences in baseline characteristics between the NGM and DM2 groups were tested with a Student *t* test for continuous variables. Postprandial triglyceride, glucose, and MPO responses were calculated as incremental (iAUC) and total area under the curve (tAUC) with the trapezoid method and expressed as mean incremental or total concentration by dividing the incremental or total response by 8 hours. Differences in postprandial MPO responses (mean tAUC and mean iAUC) between the fat-rich and the carbohydrate-rich meals were tested by a paired-samples *t* test. A one-sample *t* test with zero as test value was used to test whether the mean incremental area was different from zero (ie, no change in mean incremental MPO). Differences in postprandial time point (2, 4, and 8 hours) were tested with a paired-samples *t* test compared with baseline. Correlations between MPO and clinical and biochemical characteristics were expressed as Spearman correlation coefficients. A 2-sided P value < .05 was considered as statistically significant.

4. Results

4.1. Characteristics of the study population

Subjects with one or more missing values were excluded (n = 17), and all statistical analyses were performed on the remaining 100 subjects (66 with NGM and 34 with DM2). Subjects who were excluded from the statistical analyses did not significantly differ with respect to fasting total leukocyte count, triglycerides, and glucose (all $P > .05$, for NGM and DM2 separately). The characteristics of the 100 subjects are presented in Table 1. On average, women with DM2 were more obese and had higher fasting plasma glucose, HbA_{1c}, triglycerides, and blood pressure compared with women with NGM. No differences were observed in total cholesterol and LDL cholesterol, whereas HDL cholesterol was lower in DM2.

Table 1
Clinical and biochemical characteristics of the study population

Variable [a]	NGM	DM2	*P*
n	66	34	
Age (y)	60.5 (4.0)	58.7 (3.7)	.03
Waist (cm)	87.1 (9.8)	102.4 (14.4)	<.001
Fasting glucose (mmol/L) [b]	5.2 (0.3)	7.0 (1.3)	<.001
HbA_{1c} (%)	5.5 (0.3)	6.5 (0.6)	<.001
Total cholesterol (mmol/L) [b]	5.7 (0.8)	5.6 (1.0)	.41
HDL cholesterol (mmol/L) [b]	1.65 (0.41)	1.40 (0.30)	<.01
LDL cholesterol (mmol/L) [b]	3.5 (0.8)	3.4 (0.8)	.40
Triglycerides (mmol/L) [b, c]	1.1 (0.9-1.4)	1.5 (1.2-2.0)	<.001
Systolic blood pressure (mm Hg)	129 (14)	143 (17)	<.001
Diastolic blood pressure (mm Hg)	70 (8)	79 (7)	<.001

[a] Data are mean (SD) or median (interquartile range).
[b] Mean of the 2 meal visits.
[c] ln-transformed before analysis.

4.2. Postprandial glucose and triglycerides

Fig. 1 shows the 8-hour time courses of triglycerides and glucose after 2 consecutive fat-rich and 2 consecutive carbohydrate-rich meals. The increase (iAUC) in postprandial triglycerides was similar in women with DM2 and women with NGM after the fat-rich meals (0.9 ± 0.5 vs 0.9 ± 0.5 mmol/L, $P = .97$). The rise of plasma glucose (iAUC) levels after the fat-rich meals was higher in women with DM2 compared with the NGM women (0.7 ± 1.5 vs 0.1 ± 0.4 mmol/L, respectively; $P < .05$). After the carbohydrate-rich meals, postprandial glucose (iAUC) values were higher in women with DM2 compared with women with NGM (3.1 ± 2.7 vs 0.4 ± 0.6 mmol/L, respectively; $P < .001$).

4.3. Baseline and postprandial leukocytes and MPO

Baseline number of leukocytes was higher in DM2 compared with NGM (6.1 ± 1.4 vs 5.4 ± 1.2 × 10^9/L, respectively; $P < .05$). The number of leukocytes did not significantly increase after the carbohydrate-rich meals (from 5.0 ± 1.2 to 5.3 ± 1.3 × 10^9/L in NGM and from 5.8 ± 1.3 to 6.0 ± 1.4 × 10^9/L in DM2; $P = .07$ and $P = .23$, respectively). After the fat-rich meals, leukocytes increased from 5.0 ± 1.5 to 6.1 ± 1.5 × 10^9/L and from 5.8 ± 1.4 to 6.6 ± 1.4 × 10^9/L in NGM and DM2, respectively (both $P < .01$). The postprandial changes in MPO are presented in Fig. 2 and in Table 2. Baseline MPO (mean value of the 2 meal visits) was not statistically significantly different between NGM and DM2 (51.4 ± 12.9 and 54.5 ± 18.4 μg/L, respectively; $P = .39$). As expected, baseline MPO was positively associated with total leukocyte counts ($r = 0.20$, $P = .04$), whereas an inverse association of fasting MPO with fasting HDL cholesterol ($r = -0.22$, $P = .02$) was observed. No significant associations of baseline MPO were found with age, triglycerides, fasting glucose, total cholesterol, and systolic and diastolic blood pressure.

The MPO iAUC and tAUC after both meal types did not significantly differ between DM2 and NGM, nor did MPO at any of the time points differ between DM and NGM (all $P > .1$). The MPO iAUC was significantly different from zero in NGM (−2.5 ± 5.5 and −2.9 ± 5.3 μg/L, fat-rich meals and carbohydrate-rich meals, respectively; both $P < .01$), but not in DM2 (−1.7 ± 5.5 and −1.6 ± 5.2 μg/L, fat-rich meals and carbohydrate-rich meals, respectively; $P = .08$ and $P = .09$, respectively). Furthermore, compared with baseline, MPO was significantly lower at 8 hours after breakfast in NGM (both meal types) and DM2 (fat-rich meals only) (all $P < .05$) (Table 2).

5. Discussion

This is, to the best of our knowledge, the first study to examine postprandial MPO responses. We found no

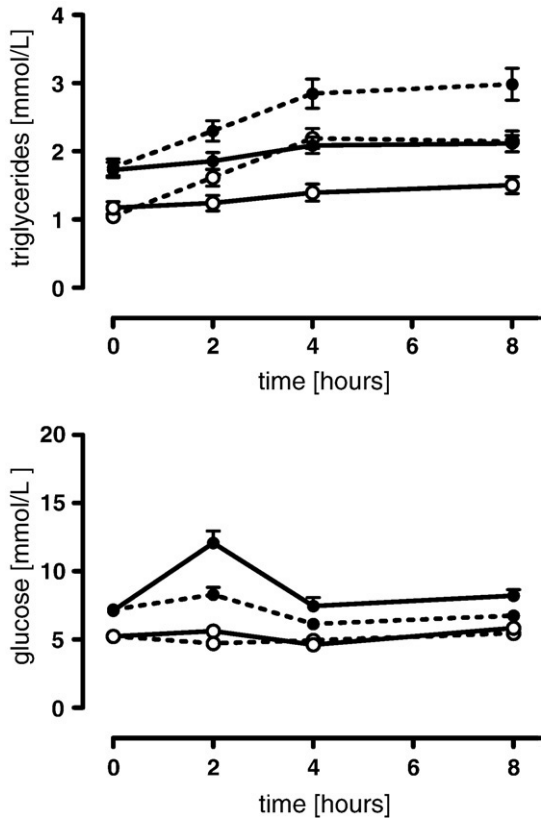

Fig. 1. Time course of triglycerides (upper panel) and glucose (lower panel) (mean ± SEM) after 2 consecutive carbohydrate-rich meals (solid line) and 2 fat-rich meals (dotted line) given at 0 and 4 hours in individuals with NGM (open dots) and patients with DM2 (solid dots).

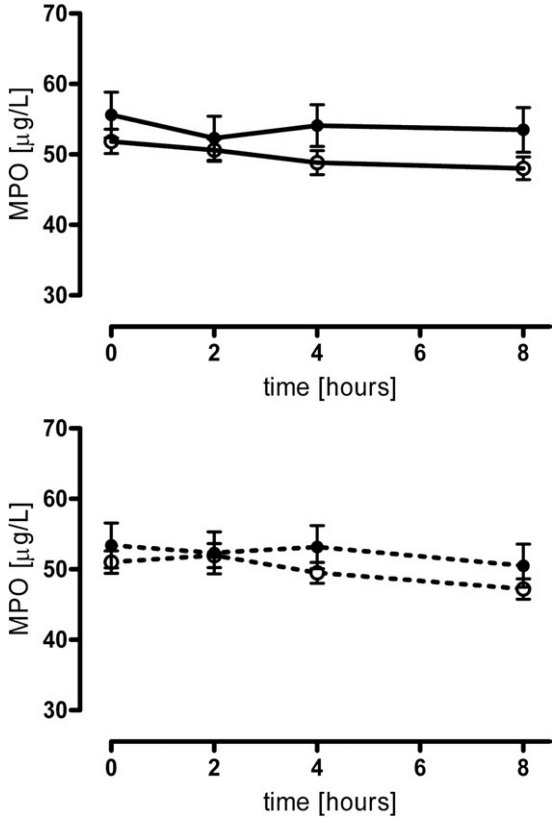

Fig. 2. Time course of MPO (mean ± SEM) after 2 consecutive carbohydrate-rich meals (solid line) (upper panel) and 2 fat-rich meals (dotted line) (lower panel) given at 0 and 4 hours in individuals with NGM (open dots) and patients with DM2 (solid dots).

significant differences in baseline MPO between DM2 and NGM. Baseline MPO was negatively related to HDL cholesterol and positively correlated to leukocyte counts. Total leukocytes increased after the fat-rich meals in both NGM and DM2, whereas MPO decreased postprandially in NGM (both meals) and in DM2 (fat-rich meals).

Previous studies have shown that leukocytes increase after a fat-rich meal [10]. In addition, one study suggested that activation markers on monocytes and neutrophils are increased and related to postprandial changes in triglycerides [9]. Furthermore, activation markers on monocytes and neutrophils were higher in DM2 as compared with healthy controls [24]. These observations suggest that postprandial leukocyte recruitment and activation may be a mechanism in the relation between postprandial derangements and increased CVD risk. In addition, a number of studies suggest that patients with higher MPO levels have an increased CVD risk [16-19]. In the present study, the number of leukocytes in the fasting blood samples was higher in DM2 as compared with NGM; but despite this, MPO was not significantly higher in DM2 as compared with NGM. This lack of difference may be explained by an impaired leukocyte function in DM2. Indeed, a previous study showed lower MPO in lymphocytes and neutrophils in patients with DM2 compared with healthy controls [25]. In contrast to our initial hypothesis, we found lower MPO values in the postprandial state after both meal types. Therefore, changes may not only be meal-induced, but also be due to diurnal changes in leukocytes and MPO. Future studies assessing diurnal MPO course in the fasting state should address this issue.

In accordance with other studies [16,26], we found a weak negative correlation between MPO and HDL cholesterol. Indeed, MPO binds to apolipoprotein AI of HDL particles and may subsequently be inactivated or excreted [27]. Furthermore, MPO may be involved in generating dysfunctional HDL and thus promote atherogenesis by this pathway [28]. In line with this conjecture, a recent study has shown that MPO is associated with progression of carotid

Table 2
Fasting and postprandial concentrations of MPO (mean, SD) in 66 women with NGM and 34 women with DM2

	Time (h)	CARB		FAT	
		NGM	DM2	NGM	DM2
MPO (μg/L)	Baseline	51.8 (14.0)	55.6 (18.9)	51.0 (13.0)	53.8 (18.4)
	2	50.6 (13.1)	52.3 (18.3)*	51.9 (13.8)	52.3 (17.4)
	4	48.8 (13.4)*	54.1 (17.2)	49.5 (12.1)	53.2 (17.8)
	8	48.0 (13.0)*	53.5 (18.5)	47.2 (12.6)*	50.5 (17.7)*

CARB indicates carbohydrate-rich meals; FAT, fat-rich meals.
* $P < .05$ vs baseline.

artery stenosis in patients with low HDL cholesterol levels [26]. Myeloperoxidase has also been shown to promote oxidation of LDL particles [29,30], which may provide another mechanism linking MPO to CVD risk.

We measured MPO in EDTA plasma instead of heparin plasma or serum. The MPO mass determined in serum is in general higher than in heparin plasma because of in vitro release of MPO from activated leukocytes [31]. For heparin plasma, it is necessary to collect the samples on ice before sample processing (ie, centrifugation) to avoid MPO release [31]. When EDTA blood was taken, we observed no changes in MPO concentrations over a period of 2 hours at room temperature before sample processing, whereas MPO rose gradually in heparin plasma as well as in blood withdrawn in tubes without an added anticoagulant (data not shown). Hence, EDTA plasma was chosen for MPO measurements because we assume that this may reflect the in vivo MPO secretion of leukocytes most precisely.

We acknowledge that our study had some limitations. First, the study population consisted exclusively of white postmenopausal women; and therefore, the results cannot be generalized to other populations. Second, because of unavailable plasma samples at 2 hours after the second meal, the present data may have underestimated the true changes in postprandial MPO. Third, our results are based on measurement of MPO mass. Although Zhang and coworkers [16] reported a high correlation between MPO mass and MPO activity ($r = 0.95$), we cannot exclude that postprandial changes in MPO activity are more pronounced than alterations in MPO concentrations. Finally, we cannot exclude the possibility that postprandial MPO release occurred but was not reflected by systemic MPO levels because of local retention or binding of MPO to tissues, including the vascular wall. Myeloperoxidase can be mobilized from vascular compartments by intravenous administration of heparin [32], but our study design precluded measurement of MPO in postheparin plasma because this approach does not allow multiple sampling and interferes with lipid metabolism.

In conclusion, we found no increase in MPO concentration despite the postprandial increase in leukocytes after the fat-rich meals, suggesting that postprandial leukocyte recruitment is likely to occur, but without a concomitant MPO release in plasma. Our findings provide no support to the initial hypothesis that meal-induced release of MPO might be a mechanism that contributes to CVD risk in postmenopausal women with NGM or DM2; and therefore, other mechanisms may link postprandial leukocytes to CVD risk.

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