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Myeloperoxidase levels predict accelerated progression of coronary atherosclerosis in diabetic patients: Insights from intravascular ultrasound

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ABSTRACT

Objective: While inflammation has been proposed to contribute to the adverse cardiovascular outcome in diabetic patients, the specific pathways involved have not been elucidated. The leukocyte derived product, myeloperoxidase (MPO), has been implicated in all stages of atherosclerosis. The relationship between MPO and accelerated disease progression observed in diabetic patients has not been studied.
Methods: We investigated the relationship between MPO and disease progression in diabetic patients. 881 patients with angiographic coronary artery disease underwent serial evaluation of atherosclerotic burden with intravascular ultrasound. Disease progression in diabetic (n = 199) and non-diabetic (n = 682) patients, stratified by baseline MPO levels was investigated.
Results: MPO levels were similar in patients with and without diabetes (1362 vs. 1255 pmol/L, $p = 0.43$). No relationship was observed between increasing quartiles of MPO and either baseline ($p = 0.81$) or serial changes ($p = 0.43$) in levels of percent atheroma volume (PAV) in non-diabetic patients. In contrast, increasing MPO quartiles were associated with accelerated PAV progression in diabetic patients ($p = 0.03$). While optimal control of lipid and the use of high-dose statin were associated with less disease progression, a greater benefit was observed in diabetic patients with lower compared with higher MPO levels at baseline.
Conclusions: Increasing MPO levels are associated with greater progression of atherosclerosis in diabetic patients. This finding indicates the potential importance of MPO pathways in diabetic cardiovascular disease.

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Diabetic patients have a markedly increased incidence of adverse cardiovascular events, in association with an extensive atheroma burden and an accelerated plaque progression [1–4]. In these patients, the combination of impaired glycemic profile with hypertension, dyslipidemia and obesity are considered to have a detrimental impact on the artery wall and lead to the development of extensive atherosclerotic plaque.

In addition to these metabolic abnormalities, increasing evidence supports a central role for inflammation in the pathogenesis of both atherosclerosis and diabetes [5–8] Previously, a greater inflammatory cell infiltration was observed on pathological examination of atherosclerotic plaques of diabetic patients [10,11]. Moreover, a positive correlation has existed between inflammation and progression of carotid intima-media thickness in diabetic subjects [12,13]. However, it remains to be fully elucidated which specific inflammatory pathways are upregulated in diabetic atherosclerosis.

Myeloperoxidase (MPO) is a pro-oxidant enzyme released from granules of activated neutrophils, monocytes, and certain tissue macrophages [14,15]. While a major biological function of MPO is the defense of the organism against infections by generating antimicrobial oxidants, free radicals and other reactive oxidant species [16,17], this activity can also lead to oxidative damage of

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; EEM, external elastic membrane; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; IVUS, intravascular ultrasound; LDL, low-density lipoprotein; MPO, myeloperoxidase; PAV, percent atheroma volume.

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endothelium and vessel wall [18,19]. MPO promotes oxidation of low-density lipoprotein (LDL) [20], and apolipoprotein A-I in high-density lipoproteins (HDL), which impairs its ability to promote reverse cholesterol transport [21–23]. MPO also directly scavenges nitric oxide, diminishing nitric oxide bioavailability leading to endothelial dysfunction [24–26]. Recent study has reported that HDL-associated MPO activity and content were increased in diabetic patients [27]. Furthermore, MPO-derived oxidants impaired the endothelial-protective effect of HDL, leading to endothelial dysfunction [27]. Given that endothelial dysfunction has been considered to associate with the development of atherosclerosis, we hypothesized that MPO may contribute to the initiation and propagation of atheromatous plaque in diabetic patients.

Intravascular ultrasound (IVUS) permits high resolution imaging of the arterial wall [28] and has been employed in clinical trials to assess the effect of various anti-atherosclerotic drugs on coronary atherosclerosis [29–31]. The purpose of the current study was to investigate the relationship between systemic level of MPO, atheroma burden and progression in non-diabetic and diabetic patients with coronary artery disease (CAD).

1. Methods

1.1. Study population

From 1184 patients in 3 clinical trials that evaluated the effect of medical therapies on the progression of coronary atherosclerosis by using IVUS,we identified and analyzed 881 patients with available serum MPO level at baseline. Of these patients, there are 682 non-diabetic and 199 diabetic patients with follow-up IVUS data. Three clinical trials analyzed in the current study were the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) study [29] the CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) study [30] and the ACTIVATE (Acyl: Cholesterol Acyltransferase Intavascular Atherosclerosis Treatment Evaluation) study [31]. These clinical trials employed serial IVUS examination to assess the impact of intensive lipid lowering, antihypertensive therapy and acyl: cholesterol acyltransferase inhibition on progression of coronary atherosclerosis. Eligibility criteria in these clinical trials included the presence of stable CAD, defined as a lumen stenosis >20% in at least one major epicardial coronary artery on visual estimation of the coronary angiogram performed for a clinical indication. Each study was approved by the institutional review boards of the participating clinical trial sites, and all participants in the trials provided informed written consent before enrollment.

1.2. Acquisition and analysis of IVUS images

The methods for acquisition and analysis of IVUS images have been described previously [29–31]. In brief, a target vessel without luminal stenosis >50% within a segment of at least 30 mm in length was selected for imaging. This vessel was required to not have undergone previous revascularization or represent the culprit vessel for a prior myocardial infarction. After anticoagulation therapy and administration of intracoronary nitroglycerin, an imaging catheter containing a high-frequency ultrasound transducer (30–40 MHz) was inserted distally within the coronary artery. Ultrasonic images were continuously recorded on videotape during withdrawal of the catheter at a constant rate of 0.5 mm/s. Imaging was performed within the same coronary artery at baseline and at the end of the study, which ranged from 18 to 24 months.

The recorded images were digitized for subsequent analysis. An anatomically matched segment was defined at the 2 time points on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. The leading edges of the lumen and external elastic membrane (EEM) were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges.

The percent atheroma volume (PAV) was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque and was selected by virtue of its strong association with clinical outcomes.

$$\text{PAV formula} \quad \text{PAV}\,(\%) = \left[\sum(\text{EEMarea} - \text{LUMENarea})/\sum \text{EEMarea}\right] \times 100$$

1.3. Biochemical analyses of MPO levels

Systemic concentrations of MPO were measured at baseline using a commercially available FDA-cleared ELISA (CardioMPO Test, Cleveland Heart Lab, Cleveland, Ohio). The inter-assay and intra-assay coefficients of variance were 2% and 6%. The lower detection limit was 13 pmol/l, and the upper detection limit was 5223 pmol/l. Samples with MPO values in excess of this were remeasured upon dilution. Spike and recovery studies with isolated human MPO into plasma matrix showed >95% accuracy [35]. Samples were analyzed in random order to avoid systemic bias by laboratory personnel, who were blinded to all clinical and laboratory phenotypic data.

1.4. Statistical analysis

Continuous variables were expressed as mean ± SD if normally distributed (or median and interquartile range if not normally distributed) and categorical variables as percentage. In non-diabetic and diabetic patients respectively, clinical characteristics, medication use and atherosclerotic plaque burden at baseline were compared across quartiles of baseline MPO levels using polyserial correlation analysis for normally distributed continuous variables and Spearman rank correlation analysis for non-normally distributed continuous variables, and Cochran–Armitage trend test for categorical variables.

Serial changes in plaque burden (expressed as least-squares mean ± SEM) across the MPO quartiles were assessed with a random effect mixed model adjusting for baseline plaque burden, in non-diabetic and diabetic patients respectively, with trial set as a random factor to control for heterogeneity across the 3 studies. A test of trend on the serial changes across the increasing MPO quartiles was also conducted within each of the patient groups. Since there was no trend in the non-diabetic patients, subsequent analyses focused on diabetic patients. A multivariable mixed model adjusting for clinical characteristics was then constructed for diabetic patients through model selection. First, covariates that were univariately contributive to the relationship of atheroma progression and MPO quartiles (with a p-value <0.10) were chosen. These covariates were further selected by bootstrap resampling (1000 iterations) and the final covariates were baseline and change in LDL-C, diastolic blood pressure and concomitant insulin use. The relationship of atheroma progression against baseline MPO was further examined in diabetic patients by checking the effect of the interactions between high-level MPO and intensive risk factor control of LDL cholesterol and high-dose statin use. A 2-sided probability value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary North Carolina).

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