ABSTRACT

Key events in the development of atherosclerosis seem to be retention of lipoproteins in the arterial wall leading to oxidative modification of LDL particles with a subsequent inflammatory reaction. Circulating oxidized LDL (oxLDL) measured in plasma has previously been related to coronary artery disease as well as to subclinical atherosclerosis progression. In the context of cardiovascular (CV) disease the metabolic syndrome (MetS) and type-2 diabetes are also of particular interest. There are conflicting data of whether newly diagnosed diabetes is related with increased subclinical atherosclerosis as compared to normal glucose tolerance. C-reactive protein (CRP) has been both linked to CV events and to the development of diabetes mellitus. However, at present it is not known whether these associations are an expression of an underlying atherosclerotic process.

In last years, a new approach in the use of ultrasound has been to study not only arterial wall thickening (Intima-media thickening, IMT), presence or absence of plaques but also the phenotype of plaques by assessing the echogenicity of the plaques. Echolucent plaques in the carotid arteries have been shown to represent the rupture prone plaque phenotype and have been shown to predict CV events.

The overall aim was to explore the role of oxLDL and hsCRP as biomarkers of metabolic disturbances and atherosclerosis in relation to occurrence of non-stenotic echolucent plaques in the carotid and femoral arteries. This was a cross-sectional population based cohort of 58-year old clinically healthy men at baseline (n=391) and at 3-years follow up we also included men on CV medication, giving at total number of n=513 subjects. Circulating oxLDL was assessed in plasma by ELISA, utilizing a specific antibody mAb-4E6. High-sensitive CRP (hsCRP) was measured in plasma by ELISA. Assessment of plaque echogenicity, by B-mode ultrasound, was based on a four-graded classification scale.

The results showed that subjects with the MetS had higher levels of oxLDL in plasma as compared to men without the syndrome (95.3 ± 26.0 U/L and 77.4 ± 22.0 U/L, $p < 0.001$). LDL peak particle size was independently associated to oxLDL (beta = -3.7 U/L, $p < 0.01$). Composite IMT of the carotid artery was thicker in newly diagnosed diabetes and established diabetes as compared with healthy controls (0.076 [95% CI 0.003-0.149] mm, and 0.163 [95% CI 0.107-0.220] mm), respectively) but IMT was not related to hsCRP. Echolucent plaques in the femoral and carotid arteries were independently associated with higher levels of oxLDL (OR=1.48, 95% CI 1.13-1.93, p=0.004 and OR=1.34, 95% CI 1.05-1.71, p=0.019, respectively), adjusted for traditional risk factors and hsCRP.

These findings underline the importance of early detection of patients with diabetes and metabolic disturbances for life style modification and medical treatment in selected cases. Data from this thesis do not support hsCRP as a useful biomarker in characterizing quantitative or qualitative aspects (plaque size and echogenicity) of preclinical atherosclerosis in the carotid and femoral arteries measured with B-mode ultrasound. Circulating oxLDL measured in plasma seems to be a marker of the small dense LDL phenotype, the metabolic syndrome and quantitative as well as qualitative measures of atherosclerosis. Additional studies are, however, clearly needed to clarify these aspects.

Key words: atherosclerosis, ultrasound, C-reactive protein, oxidized low-density lipoprotein, metabolic syndrome, type 2 diabetes, carotid artery, femoral artery, intima-media-thickness, plaque, echogenicity, risk factors

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