Studies on the atherogenicity of apoB-containing lipoproteins in type 2 diabetes

Akademisk avhandling

Som för avläggandet av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula på SU/Sahlgrenska, Göteborg

torsdagen den 5 februari 2009, klockan 13.00

av

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Fakultetsopponent: Docent Ewa Ehrenborg, Enheten för aterosklerosforskning, Karolinska universitetssjukhuset, Solna.

Avhandlingen baseras på följande delarbeten:

I. **Increased lipolysis by secretory phospholipase A_2 group V of lipoproteins in diabetic dyslipidemia**

Pettersson Camilla, Fogelstrand Linda, Rosengren Birgitta, Ståhlman Sara, Hurt-Camejo Eva, Fagerberg Björn, Wiklund Olov.

J Int Med 2008 Aug;264(2):155-65.

II. **LDL-associated proteins revealed using qualitative and quantitative proteomics – specific distribution in individuals with type 2 diabetes and the metabolic syndrome**

Pettersson Camilla, Karlsson Helen, Fagerberg Björn, Lindahl Mats, Larsson Thomas, Ståhlman Marcus, Fogelstrand Linda, Borén Jan, Wiklund Olov.

Submitted, under revision.

III. **Elevated levels of serum lysozyme in type 2 diabetes**

Pettersson Camilla, Fogelstrand Linda, Fagerberg Björn, Douhan Håkansson Lena, Borén Jan, Wiklund Olov.

Submitted.

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Type 2 diabetes (T2D) and the metabolic syndrome (MetS), two conditions that are rapidly increasing in prevalence, as well as the dyslipoproteinemia and subclinical inflammation characteristic for these conditions, are associated with an increased risk for developing and dying of cardiovascular disease (CVD). The aim of this thesis was to investigate possible atherogenic properties of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) in T2D and MetS. We compared the susceptibility to lipolysis by secretory phospholipase A_2 group V ($sPLA_2$-V) of VLDL and LDL from individuals with T2D and MetS and from healthy individuals. We also characterized LDL-associated proteins, and compared the protein composition of LDL in T2D and MetS with LDL from healthy individuals. Finally, we investigated if lysozyme, one of the proteins that was increased in T2D-MetS-LDL, was elevated in serum of individuals with T2D and MetS as well.

Lipid-enriched VLDL and small, cholesterol-poor and triglyceride-rich LDL from T2D-MetS-individuals were more extensively lipolyzed by $sPLA_2$-V than control VLDL and LDL. 31 LDL-associated proteins, important for lipoprotein metabolism, complement, coagulation, oxidation, and inflammation, were identified in LDL. VLDL and LDL from T2D-MetS-individuals contained more apolipoprotein (apo) C3 per particle, and an increased LDL-apoC3 content correlated with a lower cholesterol content of LDL and a smaller LDL-size. T2D-MetS-LDL also contained less apoA1 and more apoJ and lysozyme than did control LDL, and higher abundances of apoJ and lysozyme also correlated with a lower cholesterol content in LDL. Lysozyme was also found to be elevated in serum of T2D-MetS individuals, and lysozyme levels correlated with serum creatinine and insulin levels.

The identified LDL-associated proteins might be of importance for the inflammation following LDL retention in the intima. An increased $sPLA_2$-V-mediated lipolysis of VLDL and LDL in individuals with T2D and MetS may cause increased retention of LDL and lead to high local concentrations in the intima of proinflammatory fatty acids and lysophosphatidylcholine. This might lead to an accelerated atherosclerosis development in these individuals. An increased understanding of lipoprotein alterations in diabetes may furthermore serve as a basis for the development of new treatment strategies for atherosclerosis in T2D and MetS.

Keywords: Type 2 diabetes, metabolic syndrome, atherosclerosis, VLDL, LDL, secretory phospholipase A_2 group V, inflammation, complement, apolipoprotein, lysozyme

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