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Small dense LDL oxidation in hypertensives and diabetics and prediction of Metabolic Syndrome

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KEYWORDS
Metabolic Syndrome;
Small dense LDL;
Oxidation;
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Summary

Aim: The aim of this study is to compare the extent of small dense low-density lipoprotein (sdLDL) oxidation in diabetic and hypertensive patients and to investigate their correlation with Metabolic Syndrome as per NCEP ATP III criterion.
Design and methods: In the present study, 120 human subjects, men and women were selected randomly from the age group of 30—75 yrs for the screening of Metabolic Syndrome. Family history and prevalence of diabetes and hypertension in different age groups were recorded. Their waist circumference was measured and lipid profile was also determined. The sdLDL was isolated and oxidized in vitro. Attention was focused on the peak oxidation time of sdLDL in vitro and estimation of serum paraoxonase (PON-1) activity of all volunteers.
Results: Our results have indicated an overall increase in total cholesterol (TC), triglycerides (TGs), low-density lipoproteins (expressed as mg/dL) as well as mean waist circumference (expressed as cm) of the diabetic (242 ± 10.1, 218 ± 21.6, 140 ± 4.9, 105 ± 1.6) and hypertensive subjects (220 ± 6.4, 250 ± 12.9, 150 ± 5.6, 104 ± 1.9) as compared to controls (182 ± 5.4, 142 ± 8.9, 112 ± 4.3, 86 ± 1.5). It was also found that most of the diabetic and hypertensive subjects were from the age group of 50—59 yrs. The results obtained after oxidation of sdLDL have shown an early peak of oxidation in hypertensives [peak value = 65.3 ± 5.6 s] followed by diabetics [peak value = 75.7 ± 3.8 s]. Antioxidant enzyme paraoxonase was also found to be compromised in hypertensives and in diabetics.
Conclusion: The early peak of oxidation of sdLDL in hypertensives put them at a higher risk to CVD as compared to diabetics and abnormal lipid profile and increased waist circumference of diabetics and hypertensives suggest them to be potential patients of Metabolic Syndrome as per NCEP ATP III criterion.
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Introduction

The observation that certain risk factors accumulate in coronary patients is suggestive of a common origin and was the subject of quite early reports in clinical literature [1,2]. The concept has evolved through a number of synonyms [3] to its present status as the Metabolic Syndrome [4]. The strongest candidate for the common origin is insulin resistance [4,5]. A growing number of metabolic anomalies are linked to insulin resistance [3], the core components as excess weight, dyslipidemia and hypertension have recently been incorporated into guidelines by WHO [6] and National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) [7] to provide a definition of the Syndrome which should aid clinical studies. Insulin resistance (or indications for abnormal glucose metabolism) is the central feature of WHO definition whereas the NCEP ATP III recommendations do not require evidence of insulin resistance.

Patients with the Metabolic Syndrome have significantly decreased low-density lipoprotein (LDL)—cholesterol/apo-A1 ratio which is related to the formation of small, dense lipoprotein particles that has higher susceptibility to oxidative modifications [8]. Hypertensive patients may have a preponderance of small dense LDL (sdLDL) particles; a phenomenon associated with an atherogenic lipoprotein profile and a 3-fold increased risk of cardiovascular diseases [9]. Additional risk factors that may be associated with the Syndrome include Type-II diabetes, hyperurecemia, microalbuminuria, and coagulation abnormalities that constitute a prothrombic diathesis [10]. Several studies have found an inverse relationship between the lag time of in vitro LDL oxidation and the severity and progression of coronary atherosclerosis [11], suggesting that enhanced susceptibility to oxidation may underlie the excess vascular disease observed in patients with diabetes.

The Syndrome is also associated with reduced concentrations and activities of the antioxidant enzyme paraoxonase-1 [8]. Human serum paraoxonase (PON-1), a 43 kDa protein catalyses the hydrolysis of organophosphate esters, aromatic carboxylic acid esters and carbamates in a calcium dependent manner [12]. Although the natural substrate for PON-1 is still unknown, several groups have reported that the enzyme protein has the capacity to retard the accumulation of lipid peroxides in low-density lipoprotein (LDL) and this is mainly due to the ability of the enzyme to reduce hydroperoxides [13]. Aviram et al. [14] have shown an inverse correlation between the esterolytic activity of PON-1 in serum and susceptibility of HDL to oxidation. The Metabolic Syndrome is well characterised by the presence of smaller, denser lipoprotein particles that increase their susceptibility to oxidative modification and a diminished serum PON-1 which is a major determinant of the antioxidant capacity of HDL. These may be contributory factors to the increased presence and severity of coronary diseases in such patients [8].

We through the present study, therefore have examined the kinetics of in vitro oxidation of sdLDL after isolating it from the serum of volunteers. Attention was focused on the peak obtained for oxidized sdLDL. The arylesterase activity of PON-1 was also recorded in the respective volunteers.

Subjects and methods

A total of 120 subjects were recruited on a consecutive basis for a screening program to check the prevalence of Metabolic Syndrome at the J.N. Medical College, A.M.U. Men and women aged 30—75 yrs participated in this study. All the volunteers, unaware of their health status and not observing any medication schedule for either diabetes or hypertension, were randomly selected and divided into three categories: diabetics (those having fasting plasma glucose level $\geq$110 mg/dL but no hypertension), hypertensives (those having BP $\geq$130/80 mmHg but no diabetes) and controls (those having neither diabetes nor hypertension). Demographic information and clinical history was obtained after getting informed consent. Waist circumference of all volunteers was measured using standard techniques. Fasting blood specimens were obtained for determination of plasma glucose, serum cholesterol, serum triglycerides (TGs), serum HDL and LDL cholesterol.

Plasma glucose was determined by the glucose oxidase peroxidase method [15] and the concentration of serum cholesterol, serum triglycerides, and HDL cholesterol were measured by an enzymatic colorimetric test using commercial kits from Ranbaxy Diagnostic Division, HP. LDL cholesterol was calculated using the Friedewald equation [16].

Small dense LDL-C assay

The details and validation of this experiment have been described elsewhere [17]. In brief, the precipitation reagent (0.1 mL) containing 150 U/mL of heparin sodium salt and 90 mmol/L $MgCl_2$ was added to a serum sample (0.1 mL) and the samples were incubated for 10 min at 37 °C after mixing. Then each sample was placed in an ice-bath and allowed to stand for 15 min after which the precipitates were collected by centrifugation at 15,000 rpm for 15 min at 4 °C. The precipitates were always

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