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Relationship between plasma lipid concentrations and HDL subclasses

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Abstract

Background: It is generally accepted that different high-density lipoprotein (HDL) subclasses have distinct but interrelated metabolic functions. HDL is known to directly influence the atherogenic process and changes in HDL subclasses distribution may be related to the incidence and prevalence of atherosclerosis.
Methods: Apo-AI contents(mg/l) of plasma HDL subclasses were determined by 2-dimensional gel electrophoresis coupled with immunodetection for apo-AI. Four hundred forty-two Chinese adults subjects aged 33 to 78 years were assigned to different groups according to the third Report of NCEP (ATP III) guidelines. The subjects were first divided into 2 groups, normal and high TG, then further classified by plasma TC, HDL-C and LDL-C concentrations. The subjects were also divided into TC desirable and TC high groups.
Results: Apo-A contents of preβ_1-HDL were higher while HDL_{2b} were lower in high TG subjects vs. the corresponding normal TG subjects according to plasma TC and LDL-C concentrations. With the increase of plasma TC concentrations, apo-AI contents of preβ_1-HDL were significantly higher in high TC subgroup vs. TC desirable subgroup in normal TG subjects. With the decrease of HDL-C concentrations, apo-AI contents of HDL_{2b} tended to decrease in normal TG subjects. And, with the increases of LDL-C concentration, in normal TG subjects, apo-AI contents of preβ_1-HDL and HDL_{3b} were significantly higher and those of HDL_{2b} were significantly lower in very high LDL-C subgroup vs. LDL-C optimal subgroup. On the other hand, apo-AI contents of preβ_1-HDL and HDL_{3a} were significantly higher, while HDL_{2a} and HDL_{2b} were significantly lower in high TG and very high TG subgroup vs. normal TG subgroup within either TC desirable or TC high subjects. In a multivariate linear regression model, TG and TC concentrations were all associated independently and positively with high preβ_1-HDL; however, HDL-C were inversely associated with high preβ_1-HDL. And TG and TC concentrations were all associated independently and negetively with low HDL_{2b}, but HDL-C and apo-AI were positively associated with low HDL_{2b}.
Conclusions: With the increase of plasma TG, TC, LDL-C or the decrease of plasma HDL-C concentrations, there was a general shift toward smaller-sized HDL, which, in turn, indicates that reverse cholesterol transport might be weakened and HDL

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maturation might be abnormal. Plasma TG concentration is a more important factor than TC concentration on the changes of HDL subclass distribution. Moreover, when TG is normal and HDL-C decreased, large-size HDL particles tended to decrease.

Keywords: Apo-AI containing HDL subclasses; Triglyceride; Total cholesterol; High-density lipoprotein-cholesterol; Low-density lipoprotein-cholesterol; Two-dimensional gel electrophoresis-immunodetection

1. Introduction

Numerous clinical and epidemiological studies have firmly established an inverse relation between the risk of coronary heart disease (CHD) and the concentration of high-density lipoprotein-cholesterol (HDL-C) [1]. The HDL is responsible for reverse cholesterol transport (RCT). RCT describes the metabolism and an important antiatherogenic function of HDL, namely, the HDL-mediated efflux of cholesterol from cells of the arterial wall and its subsequent delivery to the liver and steroidogenic organs [2–5].

However, HDL has in common a high density (>1.063 g/ml) and a small size (Stoke's diameter 5–17 nm) [6]. HDL particles are composed of outer layer containing free cholesterol, phospholipids, various apolipoproteins, which covers a hydrophobic core consisting primarily of triglycerides and cholesterol esters. The majority of the HDL particles contain apo-AI [6]. Differences in the quantitative and qualitative content of lipids, apolipoproteins, enzymes and lipid transfer proteins result in the presence of various HDL subclasses, which are characterized by differences in shape, density, size, charge and antigenicity [6]. Subclasses of HDL can be separated by zonal [7] or single-spin vertical ultracentifugation [8], heparin-magnesium precipitation [9], nuclear magnetic resonance (NMR) spectroscopy [10], or 1- and 2-dimensional polyacrylamide gel electrophoresis [11–13].

Using agarose gel electrophoresis, HDL can be separated into 2 parts, i.e., preβ- and α-HDL. Pre-β part can be further distinguished by subsequent polyacrylamide gradient gel electrophoresis into preβ$_1$-, preβ$_2$-, preβ$_3$-HDL and α-HDL can be separated into 5 distinct subclasses HDL$_{3c\ 3b\ 3a\ 2a\ 2b}$, according to their increasing particle size [14,15]. Apo-AI, probably the discoid shape preβ$_1$-HDL (the smallest preβ-HDL), binds to the adenosine triphosphate-binding cassette transporter A1 (ABCA1), thus allowing the transfer of free cholesterol and phospholipidids from cells to HDL [16]. Pre-β$_1$-HDL is transformed by the activity of lecithin: cholesterol acyltranstransferase (LCAT), which esterifies the free cholesterol to form α-HDL particles, which can also be formed by diffusion of cholesterol from cell membranes and by interactions with the scavenger receptor B1(SR-B1). With the further participation of LCAT and other specific plasma factors, i.e., hepatic lipase (HL), the cholesteryl ester transfer protein (CETP) and the phospholipids transfer protein (PLTP), cholesteryl ester is concentrated into the center of the lipoprotein molecule, and HDL particle is transformed from nascent discoidal preβ-HDL to mature spherical HDL$_2$. It has been postulated that RCT indeed was the metabolic process that nascent preβ-HDL converted to mature α-HDL, following the route of preβ$_1$-HDL→preβ$_2$-HDL→preβ$_3$-HDL→HDL$_3$→HDL$_2$. Due to the important role of RCT in maintaining the cholesterol homeostasis and anti-antherosclerosis, the metabolic process of HDL and HDL subclasses distribution may directly influence the antherogenic process and change in HDL distribution may be closely related to the incidence and prevalence of atherosclerosis [17–19].

Miida et al. [25] found that the apo-AI contents of preβ$_1$-HDL in patients with hypercholesterolemia were significantly higher than those with normolipidemia. Saidi et al. [26] demonstrated that patients with mixed hyperlipidemia increased concentrations of small-sized HDL particles (HDL$_{3b}$ and HDL$_{3a}$) and decreased concentrations of large-sized HDL particles (HDL$_{2a}$ and HDL$_{2b}$) [27]. We have investigated the plasma HDL subfractions distribution in hyperlipidemic, obese, non-insulin-dependent diabetes mellitus (NIDDM) and CHD subjects by 2-dimensional gel electrophesis associated with immunodection [20–24]. We found that the characteristic of the transformation of HDL subclasses in these patients appeared to be different, whereas there was a general shift toward smaller sized HDL (preβ$_1$-HDL increased while HDL$_{2a}$ and HDL$_{2b}$ decreased), suggesting that RCT