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LDL size: does it matter?

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Summary

The atherogenic lipoprotein phenotype is characterised by a moderate increase in plasma triglycerides, a decrease in high density lipoprotein cholesterol and the prevalence of smaller denser low density lipoprotein particles. The prevalence of this partially inheritable phenotype is approximately 30% and is a feature of the metabolic syndrome associated with an increased risk for cardiovascular events. The predominance of small dense LDL has been accepted as an emerging cardiovascular risk factor by the adult treatment panel (ATP) III.

Key words: small dense LDL; atherogenic lipoprotein phenotype; coronary heart disease; diabetes

Introduction

Peak size of low density lipoprotein (LDL) particles in humans shows a bimodal distribution and can be separated into a buoyant and a dense phenotype. These phenotypes have been assigned as pattern A when large LDLs and pattern B phenotype when smaller LDL particles predominate. LDL size correlates positively with plasma HDL levels and negatively with plasma triglyceride (TG) levels. The combination of small dense LDL, decreased high density lipoprotein (HDL)-cholesterol and increased TGs is called the atherogenic lipoprotein phenotype [1]. This partially inheritable trait is a feature of the metabolic syndrome and is associated with increased cardiovascular risk. In addition, it can be influenced by physical activity, dietary and hormonal factors and hypolipdaemic medication.

Genetic and environmental influences

The prevalence of this phenotype is approximately 30% in adult men, 5–10% in young men and women <20 yrs and approximately 15–25% in postmenopausal women [1–3]. It has been shown that LDL size is genetically influenced with an inheritability ranging from 35–45% based on an autosomal dominant or codominant model with varying additive and polygenic effects [4]. Thus, non-genetic and environmental factors influence the expression of this phenotype [5]. An increase of small dense LDL has been shown for abdominal adiposity [6] and oral contraceptive use [7]. Dietary factors are also of importance. It has been shown that a very low fat, high carbohydrate diet can induce the pattern B phenotype in persons genetically predisposed to this phenotype [8]. In addition, the pattern B phenotype is commonly found in familial combined hyperlipidaemia [9], hyperapobetalipoproteinaemia [10] and hypoalphalipoproteinaemia [11].

Heterogeneity of apoB containing particles

It is commonly accepted today that apolipoprotein B particles do not comprise a population with continuously variable size, but are made up of multiple subclasses with discrete size and density, different physicochemical composition and different metabolic behaviour. Based on their characteristic appearance in analytical ultracentrifugation and gradient gel electrophoresis distinct subclasses of very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and LDL particles have been defined. There are at least two subclasses of VLDL, two subclasses of IDL and seven subspecies of LDLs from large LDL I to very small LDL IVB [12]. Size differences of VLDL particles

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are mainly due to changes in core TGs while the coat consisting of apolipoproteins, free cholesterol and phospholipids is of relatively constant thickness. LDL subclasses show differences in the surface lipid content and certain features of the apolipoprotein B100 structure probably contribute to size changes in these particles [13].

Metabolism

It has been suggested that there are parallel metabolic channels within the delipidation cascade from VLDL to LDL. A metabolic relationship between large VLDL particles and small LDL particles has been demonstrated using stable isotopes in subjects with a predominance of small dense LDL [14]. Kinetic analysis of tracer studies in humans demonstrate that LDL particles show an initial rapid plasma decay, which is due to both intra-extravascular exchange and catabolism of LDLs. These studies have not yet identified the specific precursors of individual LDL subclasses, however there are data from animal models suggesting that separate pathways may be responsible for the generation of distinct LDL particles. Inverse correlations of changes in large LDL (LDL-I) and small LDL (LDL-III) and of changes of medium sized LDL (LDL-II) and very small LDL (LDL-IV) in dietary intervention studies raise the possibility of precursor-product relationships between distinct LDL subclasses [12]. Activity of lipolytic enzymes is related to the size of LDL particles. A significant inverse relationship between post-heparin lipoprotein lipase activity (LpL) and small dense LDL has been demonstrated and increases of LpL by a high fat diet was associated with an increase of large LDL and decrease of small dense LDL. Reduced activity of LpL and increased activity of hepatic lipase has been shown in subjects with the pattern B phenotype [15]. Hepatic lipase (HL) has a higher affinity for LDL than LpL and is positively correlated with plasma TGs, apolipoprotein B, mass of large VLDL and small dense LDL, but not with the mass of large LDL [16], suggesting an important role for HL in the lipolytic conversion of these particles [17]. The strong relationship of LDL size and TGs is based on their importance as substrates for the size reduction of LDL particles. By exchange of cholesteryl esters with TGs, LDL and HDL can become TG-enriched and can be further processed by lipases. Profound changes in the physicochemical composition of both LDL and HDL particles with increasing triglyceridaemia, while core cholesterol esters are progressively depleted and replaced by TG molecules have been described by Deckelbaum et al. [18]. In addition, the production of large TG rich VLDL 1 is dependent on TG availability and VLDL 1 is associated with smaller denser LDL particles (reviewed in [12]) Cholesteryl ester transfer protein (CETP) probably has an important role in the remodelling of larger to smaller LDL particles by mediating TG enrichment of IDL and large LDL [18]. In type 2 diabetes patients it has been demonstrated that CETP contributes significantly to the increased levels of small dense LDL by preferential cholesteryl ester (CE) transfer from HDL to small dense LDL, as well as through an indirect mechanism involving enhanced CE transfer from HDL to VLDL 1 [19].

Atherogenicity of small dense LDL

Several reasons have been suggested for atherogenicity of small dense LDL. Smaller, denser LDLs are taken up more easily by arterial tissue than larger LDLs [20], suggesting greater transendothelial transport of smaller particles. In addition, smaller LDL particles may also have decreased receptor-mediated uptake and increased proteoglycan binding [21]. Sialic acid, perhaps because of its exposure at the LDL surface, plays a determinant role in the in vitro association of LDL with the polyanionic proteoglycans [22] and it has been shown that sialic acid content of LDL particles of subjects with the pattern B phenotype is reduced. Further, it has been shown that oxidative susceptibility increases and an antioxidant concentration decreases with decreasing LDL size [23]. Altered properties of the surface lipid layer associated with reduced content of free cholesterol [24] and increased content of polyunsaturated fatty acids [25] might contribute to enhanced oxidative susceptibility of small dense LDL. Recently [26] we have chosen the model of apoB transgenic mice to evaluate the kinetic behavior of human LDL particles of different size in vivo in a genetically homogeneous recipient avoiding other metabolic differences that could influence LDL metabolism. We found that small LDL particles have intrinsic features that lead to retarded metabolism and decreased intra-extravascular equilibration compared to medium sized LDL. These properties could contribute to greater atherogenicity of small dense LDL.

The atherogenic lipoprotein phenotype and insulin resistance

The risk factors of persons with the pattern B phenotype are very similar to that found in the insulin resistance syndrome and the atherogenic lipoprotein phenotype can be added to the group of changes described as metabolic syndrome. It has been demonstrated that subjects with predominance of small dense LDL have a greater than two fold increased risk for developing type 2 diabetes mellitus, independent from age, sex, glucose tolerance and body mass index. An increase of peak LDL size was associated with a 16% decrease in risk of developing type 2 diabetes mellitus[27]. The link between the atherogenic profile and diabetes mellitus type 2 is explained by the effects of insulin and TGs on VLDL production and secretion, and the resulting lipolysis of larger LDL particles to smaller denser LDL particles [28]. Thus, increased serum TG concentrations are probably the main factor in size reduction of LDL particles. Importantly hyperinsulinaemia stimulates hepatic lipase, which is important for lipolysis of larger to smaller LDL particles.

The atherogenic lipoprotein phenotype and coronary heart disease

The atherogenic lipoprotein phenotype is associated with an approximately three fold increased risk for coronary artery disease (CAD) [29]. In a nested case control study of myocardial infarction during 7 years in patients of the physicians health study cases had significantly smaller LDL size than controls matched for age and smoking. However, LDL size was not an independent risk predictor after adjustment for TGs [30]. In the prospective Stanford Five City Project the association of the incidence of fatal and nonfatal CAD with LDL diameter has been investigated. The significant difference in LDL size between cases and controls was independent of levels of HDL-cholesterol, non-HDL cholesterol, TG, smoking, systolic blood pressure and body mass index, but not independent from the ratio of total cholesterol to HDL-cholesterol. In this study, LDL size was the best differentiator of CAD status in logistic regression analysis [31]. In the Quebec Cardiovascular Study the association between LDL particle size and incident ischaemic heart disease has been analyzed based on data from the entire population-based, prospective cohort of men initially free from coronary heart disease (CHD) with a follow up of five years. In this study, small dense LDL particles predicted the rate of CHD independent of LDL cholesterol, TGs, HDL cholesterol, apolipoprotein B and the total cholesterol to HDL cholesterol ratio. Further, the increase in cardiovascular risk attributed to lipid risk factors was modulated to a significant extent by variations in LDL particle size [32]. In addition, the cholesterol concentration in small dense LDL particle may give even more precise information. Again, in the Quebec heart study, St. Pierre et al. demonstrated that the cholesterol concentration in small dense LDL particles showed the strongest association with the risk of CHD. Multivariate logistic and survival models indicated that the relationship between LDL cholesterol levels in particles with a diameter <255 Å and CHD risk was independent of all nonlipid risk factors and of LDL cholesterol, HDL cholesterol, TG, and lipoprotein(a) level [33]. These data suggest that the cholesterol within small dense LDL is particularly harmful. Therefore measurement of LDL particle size and possibly cholesterol content within these particles may enhance our capability to predict cardiovasular events.

In a population of 98 man <50 years and 100 women <50 years who underwent elective diagnostic coronary arteriography, smaller denser LDL were associated with CAD independently of traditional risk factors (age, sex, smoking, diabetes, LDL and HDL cholesterol concentrations) other than plasma TGs. These results stress the importance of TGs and small dense LDL in premature CAD [34]. Taken together these studies suggest that LDL size is an important predictor of CAD. However, in most studies LDL size was not completely independent of traditional lipids especially TGs. This is not surprising as these parameters are obviously metabolically linked. Mykkänen et al. found that LDL size was not a predictor of CHD events in elderly men and women after controlling for diabetes status [35]. The main reason for the discrepancies might be a survival bias due to old age in these Finnish subjects. Further, Finnish subjects had relatively high LDL cholesterol and total cholesterol. Therefore, the power to detect effects of LDL size on CHD events might have been diminished. Interestingly, a recent study analyzing data from the CARE trial in a prospective nested case control study found that larger LDL size after adjustment for other variables was an independent predictor of recurrent coronary events in a population with CAD [36]. However, in this study cases and controls were closely matched for prevalence of LDL subclass pattern B (approximately 40%). Thus, the population was one in which the atherogenic lipoprotein phenotype did not discriminate risk for recurrent events, and in this context a strong risk associated with larger LDL was detected. Interestingly, significantly larger LDL and HDL particles have been found in Ashkenazi Jews with exceptional longevity compared to an age-matched control group. Larger LDL particles in this study were associated with a lower prevalence of hypertension, cardiovascular disease, metabolic syndrome and increased homozygosity for the I405V variant in CETP [37].

Effects of hypolipidaemic treatment on LDL size

Hypolipidaemic treatment is capable of altering LDL subclass distribution. Particularly medication with TG lowering effects will shift LDL peak size from smaller denser to larger more buoyant particles. As explained in more detail above, reduced availability of TG rich-VLDL particles leads to a reduction in the production of small dense LDL. This has been shown for fibrates (e.g. fenofibrate [38], gemfibrozil [39]) and niacin [40]. These substances preferentially lower small dense LDL, so that LDL peak size shifts to larger particles. Statins potentially lower large, medium and small LDL particles. Thus, the net effect of statins on LDL size is none or only a moderate one to larger LDL particle size. These effects are observed particularly in those substances that also have substantial effects on TGs as for example atorvastatin [41]. There are few intervention studies addressing LDL size and change in coronary stenosis. In the Familial Atherosclerosis Treatment Study (FATS) subjects with known CAD were treated with intensive lipid-lowering therapy and coronarangiography was performed at baseline and after 2.5 years. Interestingly, an increase in LDL size was most strongly associated with CAD regression, accounting for 37% of the variance of change in coronary stenosis [42]. In the Diabetes Atherosclerosis Intervention Study (DAIS) treatment with fenofibrate in patients with diabetes type 2 resulted in significant less progression of CAD and a greater increase of LDL particles compared to placebo and the authors concluded that the observed change of LDL size might have accounted in part for the beneficial action of fenofibrate [43].

Conclusions

Taken together, LDL size has been classified as an emerging cardiovascular risk factor by the adult treatment panel (ATP) III. Small dense LDL size is a strong predictor of cardiovascular events and progression of CAD. Furthermore, hypolipidaemic treatment is able to increase LDL particle size and the increase of LDL size correlates with regression of coronary stenosis. Clinical studies demonstrating that certain hypolipidaemic treatments are beneficial in persons with a predominance of small dense LDL and normal or moderately elevated cholesterol will be necessary to justify the measurement of small dense LDL in daily clinical practice.

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