Treatment of Small Dense LDL

Gen Yoshino¹, Tsutomu Hirano², and Tsutomu Kazumi³

¹Department of Laboratory Medicine, Toho University School of Medicine, Tokyo, Japan.
²First Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan.
³Department of Food Science and Nutrition, School of Human Environmental Science, Mukogawa Women’s University, Hyogo, Japan.

The increased frequency of small, dense LDL is associated with the risk of coronary heart disease (CHD). Possible mechanisms include the increased susceptibility of small, dense LDL to oxidation and its high affinity for LDL-receptor-independent cell surface binding sites. Although more than 30% of adult men in the USA have been reported to have small, dense LDL, only 5.4% of young Japanese men are affected. However, more than 76% of Japanese diabetics with coronary heart disease have small, dense LDL. Furthermore, almost half of all obese women (BMI > 35 kg/m²) have small, dense LDL. Our previous observation revealed that type 2 diabetics had smaller LDL even if they were apparently normolipidemic. In the normotriglyceridemic group, there was also a close relationship between LDL size and plasma triglyceride. Diabetics with microalbuminuria had smaller LDL than those with normal albuminuria, indicating the early nephrotoxicity of small, dense LDL. We also found that young men with high-normal blood pressure have smaller LDL than those with optimal blood pressure. Furthermore, LDL size was decreased not only in preeclamptic women but also in normal pregnant women. Finally, weight reduction by obese women through strict diet control, the treatment of diabetics by acarbose or troglitazone, and the treatment of hyperlipidemia by new statins as well as fibrates were all successful in increasing LDL size associated with decreased plasma triglyceride. J Atheroscler Thromb, 2002; 9: 266-275.

Key words: Small, dense LDL, Triglyceride, Type2 diabetes, Obesity

Introduction

A number of cross-sectional studies have shown that a predominance of small, dense LDL particles is associated with the presence of CHD (1-3). Furthermore, recent prospective studies have demonstrated that LDL size abnormalities preceded the onset of CHD (4-6). The increased frequency of small, dense LDL has also been shown to be associated with many genetic and environmental factors in addition to marked changes in serum lipoprotein and lipid levels, such as elevated triglyceride concentrations and reduced HDL-cholesterol levels (1-3). Also, a number of potential atherogenic mechanisms in the appearance of small, dense LDL have been proposed. These include the association of these particles with an atherogenic lipoprotein phenotype (7), the increased susceptibility of small, dense LDL to oxidation (8-10), the conformational difference of the apolipoprotein B molecule on small LDL particles and the possible reduction in the affinity of these particles for the LDL receptor (10,11). It is also of interest that LDL size is deeply involved in insulin resistance syndrome (12). Therefore, in this paper we demonstrate the effect of plasma triglyceride levels, blood pressure, weight reduction, the association of type 2 diabetes, especially with nephropathy, in the Japanese population, and treatment with acarbose, troglitazone, doxazosin, and fluvastatin on LDL size.
Measurement of LDL size

Plasma LDL comprises multiple discrete subclasses, differing in size and density. Initial studies conducted by Krauss and Burke (13) demonstrated that two distinct LDL subclass phenotypes can be distinguished on the basis of the LDL size distribution separated by gradient gel electrophoresis (GGE). Pattern A consists of a major peak greater than 25.5 nm, whereas in pattern B this is less than 25.5 nm. GGE preceded by density gradient ultracentrifugation, a well-established method for the separation of LDL subfractions, is time consuming and technically demanding, although it is precise. Recently, a new method has been developed for the estimation of LDL size. This new method employs continuous disc polyacrylamide gel electrophoresis (Lipoprint System LDL, Quantimetrix Co, USA) (14) and the LDL peak particle diameter (PPD) can be measured by this system. Briefly, fresh serum (25 μl) was placed in glass gel tubes and then a loading gel (200 μl) containing 0.36 mg/ml Sudan Black B was added to the tube and mixed with the samples. The loading gel is polymerized using a fluorescent light for 40 min and then electrophoresed at a constant current of 3 mA/tube until the distance between the VLDL and HDL bands is exactly 30 mm (for = 70 min), because the mobility of the HDL fraction depends on its particle size and, hence, varies. The gel in the glass tube was scanned directly at a wavelength of 610 nm (EKDS Kayagaki, laser densitometer, ADC-20EX, Kayagaki, Co, Tokyo). Different LDL subfractions can be identified by their migration distance. Each LDL subfraction has a specific electrophoretic mobility (RF) relative to the HDL fraction using the VLDL fraction at the origin of the separating gel and the HDL fraction at the end of the gel. Although seven LDL subfractions can be detected by this method, we employed the RF at the highest peak of LDL bands as the peak size of LDL particles. As there was an excellent correlation between RF obtained by this method and the peak LDL size obtained according to the method by Krauss and Burke (13) (R = 0.85, p < 0.001, r = 41), LDL-peak particle diameter (PPD) was estimated from the following equation: LDL-PPD = (1.429-RF) x 25 (Fig. 1). In eight normolipoproteinemic healthy volunteers and eight hypercholesterolemic otherwise healthy subjects, we measured the size distribution of the LDL particle using electron microscopy. These studies were carried out on lipoproteins with densities between 1.019 and 1.063. The lipoproteins were isolated ultracentrifugally and prepared for electron microscopy. For each sample, 200 particles were measured and the frequency distribution of all particles recorded. LDL-PPD measured using an electron microscopy was similar (R = 0.61) to that obtained using the continuous electrophoresis (14).

Plasma triglyceride and LDL size

It is well recognized that the most powerful determinant of LDL size is plasma triglyceride level (Fig. 2). Indeed, our previous observation revealed that LDL size can be influenced by plasma triglyceride level in almost the normal range (14). In a prospective study (5), which tested whether the predominance of small, dense LDL and increased triglyceride levels is an independent risk factor for myocardial infarction, LDL pattern B was found in 47% of men who subsequently developed myocardial infarction, whereas it was found in 35% of men who did not develop myocardial infarction. In contrast, LDL pattern B was found in only 5.4% of young healthy men who were nonobese, normolipidemic and normotensive (14). The striking differences between the two studies were in plasma triglyceride levels and body mass index (BMI) in addition to age. A low prevalence of LDL pattern B in young Japanese men may be due to low serum triglyceride levels in this population and may be compatible with the observation in Japanese men that phenotype B was found in 10% of non-diabetic control subjects whereas it was found in 48% of type 2 diabetic patients (15).

Type 2 diabetes and LDL size

A predominance of small, dense LDL (16,17) has recently been reported in diabetic subjects (18,19). In the previous study we examined the cholesterol-loading of LDL from type 2 diabetics with normolipidemia (20). In their LDL fraction, the cholesterol concentration was similar to that of the non-diabetic control group. However, because LDL-apoB was significantly increased in the diabetic subjects, their cholesterol/apoB ratio was suppressed. Our study demonstrated a significantly suppressed cholesterol/apoB ratio in the LDL fraction of strictly normolipidemic diabetic subjects. As the ratio represents the cholesterol-loading of LDL particles, and also indicates its particle size, we conclude here that LDL particles are cholesterol-depleted (small sized) in Japanese normolipidemic diabetics. This may support the report indicating the predominance of small, dense LDL in diabetic subjects (19,20). The significant increase in LDL-apoB, reflecting an increased number of LDL particles in normolipidemic diabetics, is also an important finding. One explanation for this phenomenon may be a prolonged residence time of LDL particles in the circulation because of apolipoprotein glycation (21).

Furthermore, several laboratories have recently shown that small, dense LDL displays enhanced susceptibility to copper transition metal-induced oxidation when compared with larger, buoyant lipoprotein particles (22-24). Since it is well known that oxidized lipoproteins are atherogenic (25-27), our findings here could be another reason for the increased risk of CHD in diabetic subjects even if they are apparently normolipidemic. On the other hand, Abate et al. (28) reported that there is increased cholesterol concentration in the LDL fraction of normolipidemic patients with mild type 2 diabetes. One explanation for the dis-
crepancy between these two conflicting results may be
patent selection, i.e., our study included Japanese
diabetic only and the subjects’ plasma triglyceride was
limited to below 130 mg/dl, while their patients’ upper limit
of plasma triglyceride was 250 mg/dl.

Determinants of LDL particle size including genetic
factors.

The main determinants of particle size can be classified
as biological (age, sex, genetic factors and pregnancy),
insulin resistance (obesity, diabetes mellitus),
hypertriglyceridemia, and AIDS (29). \( \beta \)-adrenergic recep-
tor blockers can also decrease LDL size(30). However,
the most powerful determinant of LDL size may be plasma
triglyceride level (5). We carried out a stepwise multiple
regression analysis to study the determinants of LDL par-
ticle size in young, nonobese, normolipidemic men. The
preliminary model included triglyceride, HDL cholesterol,
apoipoprotein A I, BMI, percent body fat, fat mass, sys-
tolic and diastolic blood pressure, and smoking status as
the independent variables. Triglyceride was the major
determinant of LDL size. Although percent body fat and

apo A I were significantly associated with LDL size, the
association between HDL-cholesterol and LDL size did
not reach statistical significance. When apoB was added
to the above model, apoB was the major determinant of
LDL size. Percent body fat appeared to be an indepen-
dent determinant in this model. It is noted that the asso-
ciation between triglyceride and LDL size was weak and
was no longer significant. When apoB, total and LDL-
cholesterol were added to the model, apoB concentra-
tion was again the major determinant of LDL size.

The inheritance of small LDL was previously reported
as autosomal dominant with variable penetration ac-
cording to age and sex (31). Eighty relations at a kibbutz were
studied for small LDL inheritance (32). The major gene
accounted for 12% of the variance in LDL species and
polygenic factors for 65% at the age of 20 years, whereas
late in life it accounted for 47% and polygenic factors for
39%. A study of 19 families (33), found that dominant
inheritance has an age-dependent penetration: in young
men and women the prevalence of small LDL was 0.17
and 0.21, but in older men and women, it was 0.82
and 0.95, respectively. Nine candidate genes (Mn super ox-
ide dismutase, apolipoproteins C III, A II, C II, LPL, hep-
atic lipase, microsomal tracylglycerol transfer protein
(MTP), insulin receptor, and LDL receptor) were ex-
amined but none were linked to small LDL. On the other
hand, a genome-wide search was performed using 331
microsatellite markers in 470 subjects (33). Major quanti-
tative trait loci for small LDL were identified on chromo-
somes 3 (including apolipoprotein D) and 4 (including
MTP) with another possible locus on chromosome 6.
Larger LDL particles were possibly linked with genes on
chromosome 19, which may involve the LDL receptor.

Mechanisms for the generation of small,dense LDL

Since the most powerful determinant of LDL size may
be plasma triglyceride level (5), it is easy to speculate that
abnormal triglyceride metabolism is deeply involved in the production of small, dense LDL. The association of small, dense LDL and insulin resistance syndrome (12) or type 2 diabetes (18,19) is well known. Both pathogenic conditions may result in the elevation of plasma free fatty acid; triglyceride and/or glucose. Under such conditions the liver will produce and release triglyceride-rich VLDLs which can be a good substrate for small, dense LDL. Packard et al. (34) proposed that triglyceride-enriched LDL is hydrolyzed by endothelium-bound hepatic lipase, an enzyme that has phospholipase as well as lipase activity, leading to the generation of lipid-depleted LDL particles with smaller size. The deficiency in cholesteryl ester transfer protein (CETP) in plasma may also contribute to the generation of small, dense LDL.

Small, dense LDL and CHD

An investigation of LDL subfractions in normotriglyceridemic men revealed that small sized LDL can be a coronary risk factor in subjects without hypertriglyceridemia (35). LDL composition was examined in diabetic, myocardial infarction survivors. Decreased cholesterol-loading in LDL and an increased number of LDL particles were also remarkable in this group of patients, indicating the predominance of small, dense LDL in myocardial infarction survivors with type 2 diabetes (36).

To examine how the prevalence of the small dense LDL phenotype (LDL particle diameter < 25.5 nm) is associated with CHD in type 2 diabetic and non-diabetic Japanese men, an ethnic group with a low incidence of CHD, 85 non-diabetic men and 45 type 2 diabetic men with angiographically documented CHD, and 142 control men and 76 type 2 diabetic men without CHD were studied (37,38). The mean LDL particle diameter was determined using 2-16% polyacrylamide GGE. LDL particle diameters in CHD patients were much smaller than those in the controls (25.2 ± 0.7 vs. 26.0 ± 0.4 nm, mean ± S.D., p < 0.0001). LDL size was smaller in diabetic subjects (25.6 ± 0.6 nm) and became even smaller in diabetics with CAD (25.0 ± 1.0 nm). The prevalence of small dense LDL was markedly higher in both non-diabetic and diabetic CHD patients than in non-diabetic and diabetic patients without CHD (71, 76, 23 and 42%, respectively). CHD patients had lower HDL-cholesterol and apo A1 levels, and higher triglyceride levels than those in diabetic and non-diabetic CHD-free patients, while total- and LDL-cholesterol levels were even lower in the CHD group, and remnant-like particle (RLP)-cholesterol, lipoprotein (a) and insulin levels were comparable among the four groups. LDL size was significantly associated with triglyceride, HDL-cholesterol and glycemic control. Logistic regression analysis revealed that the small, dense LDL phenotype was significantly associated with the incidence of CHD, independent of low levels of HDL-cholesterol or high levels of triglyceride in both non-diabetic and diabetic cases. These results suggest that the high prevalence of small, dense LDL is a leading cause of CHD in both diabetic and non-diabetic Japanese men. Type 2 diabetes shows a greater capacity to reduce LDL size, which may contribute to the high incidence of CHD in the diabetic population.

Small, dense LDL and diabetic nephropathy

The development of diabetic nephropathy is now a serious social problem not only in Western countries but also in Japan. Diabetic control is usually worse, the duration of diabetes is longer and dyslipidemia is more common in diabetic nephropathy compared with diabetes without nephropathy. Therefore, it is possible that the prevalence of small, dense LDL is substantially higher in diabetic nephropathy. Thus, to determine whether decreased LDL size is associated with an elevated incidence of CHD in diabetic nephropathy, we measured the LDL particle size in type 2 diabetic patients with various degrees of albuminuria (n = 85) and age-, weight-matched non-diabetic control subjects (n = 31). The diabetic subjects were divided into three groups, normoalbuminuric, microalbuminuric and macroalbuminuric diabetics, based on the amount of albuminuria. The average diameter of LDL particles was determined by non-denaturing polyacrylamide GGE (2-16%) (13). The plasma lipid and lipoprotein concentrations were comparable between the non-diabetic controls and normoalbuminuric diabetics, whereas the plasma triglyceride, VLDL or LDL concentration was significantly increased in diabetic nephropathy. The mean LDL particle size was significantly smaller in microalbuminuric diabetics compared with the controls or normoalbuminurics, and the LDL size was further decreased in macroalbuminurics (Fig. 3) (39). The incidence of small LDL (diameter < 25.5 nm) was remarkably increased in microalbuminuric (58%) and macroalbuminuric diabetics (67%) compared to the control (13%) and normoalbuminuric diabetics (27%). Corresponding to the decreased LDL size, the cholesterol content of the LDL was significantly depleted in diabetics with nephropathy. The high prevalence of small, dense LDL in diabetic nephropathy was also observed even when hypertriglyceridemic or hypertensive subjects were excluded from each group. The increment in triglyceride-rich lipoprotein (d < 1.006) after oral fat-loading was increased, and postheparin lipoprotein lipase activity was decreased significantly in diabetic nephropathy. These abnormalities were significantly associated with LDL particle size. Multivariate regression analysis revealed that the amount of albuminuria was closely associated with the average LDL particle size, and this association was independent of the plasma triglyceride level. Neither insulin resistance nor glycemic control was directly associated with LDL particle diameter. Thus, LDL particles become smaller in early diabetic nephropathy, and this may be associated with the
nephrotoxicity of small, dense LDL.

**Hypertension and LDL size**

We also found that young men with high-normal blood pressure have smaller LDL size than those with optimal blood pressure (40). One-hundred and ninety-eight male students had anthropometry, blood pressure, and blood tests including LDL size. As compared with 90 men with optimal blood pressure, 46 men with high-normal blood pressure had increased BMI, percent body fat and serum leptin. In addition, they had greater serum insulin and HOMA R and smaller LDL size. Since insulin resistance is deeply involved in the pathogenesis of hypertension, stronger insulin resistance in this group might impair triglyceride metabolism, thereby contributing to the appearance of smaller sized LDL.

**Obesity and LDL size**

LDL size can also be influenced by obesity (19). We observed the effect of weight reduction on LDL size in 38 obese women (BMI: higher than 32 kg/m²) including 5 type 2 diabetics with an average age of 46.3 ± 6.6 years. Seventeen of 21 subjects had small sized LDL estimated by continuous disc polyacrylamide gel electrophoresis (Lipoprint System LDL). The RLP fraction was separated by an affinity column containing anti-apoA1 and anti-apoB100 monoclonal antibodies as mixed gels (41). This enabled us to obtain lipoproteins with apoB48 only, which can be classified into RLP fraction if the samples are obtained after overnight fasting.

The average decrease in energy intake was approximately 500Kcal/day. They lost weight (4.3 ± 1.2 kg at the 1st month and 6.2 ± 2.4 kg at the 3rd month) after diet instruction and/or mazindol treatment (0.5 mg/day). In 5 diabetics, both fasting blood glucose and HbA1c were decreased significantly from the 1st month. Although there were no significant changes in plasma lipids including cholesterol, triglyceride, HDL-cholesterol, apolipoprotein (apo) A1 and apo E, RLP-triglyceride was decreased and LDL size was increased significantly during the observation period (Fig. 4,5). The mechanisms whereby LDL size was increased after weight reduction is still unclear. However, since the change in LDL size was accompanied by decreased RLP-triglyceride which is known to be of mainly intestinal origin, it is speculated that the amount and composition of lipoproteins derived from the intestine were influenced by the diet, and VLDL particles lost triglyceride content which might result in the appearance of normal sized LDL.

**Pregnancy, preeclampsia and LDL size**

It is known that serum lipid levels increase during pregnancy (42) and rapidly decrease after delivery. The plasma lipids in preeclamptic women are further increased compared with normal pregnant women (43). The dysfunc-

---

*Fig. 3.* LDL size and diabetic nephropathy (39). Vertical bars and columns represent LDL size and frequency of small, dense LDL (pattern B), respectively, micro: patients with microalbuminuria, macro: patients with overt albuminuria, *"significantly different from non-diabetic controls and diabetics with normalalbuminuria (p < 0.05), **"significantly different from all other groups (p < 0.05) by one-way ANOVA (LDL size) and by χ²-square test (frequency of pattern B).*

*Fig. 4.* Effect of weight reduction (by mazindol) in obese women on plasma total- and RLP-triglyceride. *"p < 0.05 vs 0 month value.

*Fig. 5.* Effect of weight reduction (by mazindol) in obese women on plasma LDL size. Open and closed circles indicate the data from subjects with small, dense LDL and normal sized LDL, respectively before weight reduction. Rf = 0.400 corresponds to LDL size = 25.7 nm. *"p < 0.05 vs 0 month value. Note the reciprocal changes in RLP-triglyceride and LDL size during weight reduction.
tion of maternal vascular endothelium that may be induced by hyperlipidemia during pregnancy occurs in preeclampsia (44). However, the precise mechanisms responsible for endothelial dysfunction in preeclampsia remain to be clarified. It was also reported that small, dense LDL might contribute to endothelial dysfunction in preeclampsia (45). Moreover, a previous study demonstrated that small, dense LDL in preeclamptic women might affect endothelial cells in a similar way as in the pathogenesis of atherosclerosis. These findings suggest that the appearance of small, dense LDL during pregnancy may be associated with the occurrence and development of preeclampsia. Therefore, we examined whether serum lipids changes during pregnancy and postpartum were accompanied by changes of LDL size not only in preeclamptic women but also in normal pregnant women (46) (Fig. 6). The LDL size in normal pregnant women was decreased during pregnancy and at 37 weeks of gestation showed a significant decrease compared with that of women at the 4th week after delivery (25.8 ± 1.0 vs 26.8 ± 0.7 nm, p < 0.05). LDL size in preeclamptic women at admission (mean gestational age: 36 ± 2.4 weeks) was significantly decreased compared with normal pregnancy at 37 weeks of gestation (24.7 ± 1.2 vs 25.8 ± 1.0 nm, p < 0.05). Moreover, LDL size in preeclamptic women was significantly increased after delivery compared with the level at admission (27.5 ± 0.7 vs 24.7 ± 1.2 nm, p < 0.05) accompanied by an improvement in the plasma lipid profile. These findings suggest that the predominance of small, dense LDL, a potential contributor to endothelial dysfunction, may be a possible predictor of preeclampsia.

Treatment of small, dense LDL

i) Effect of troglitazone on LDL size

It is still unknown whether insulin resistance or other factors related to insulin resistance directly regulate LDL size. We evaluated the direct association between insulin resistance and LDL size by treating patients with troglitazone (47) which ameliorates insulin resistance in patients with type 2 diabetes mellitus. In this study we treated 30 type 2 diabetic subjects under stable control with sulfonfonyurea and/or diet. The plasma levels of fasting glucose, hemoglobinA1c, and insulin were all suppressed significantly after 400 mg/day of troglitazone for 3 months. The average LDL particle diameter measured by GGE (13) was remarkably enlarged (Fig. 7), and the number of patients with pattern B (LDL diameter less than 25.5 nm) reduced from 13 to 1. An excellent correlation between increased LDL size and decreased plasma triglyceride was found (r = −0.58) during troglitazone treatment. LDL size did not correlate with blood glucose, hemoglobinA1c, or insulin levels. This may suggest that LDL size is more directly influenced by triglyceride metabolism than insulin sensitivity itself. Thus, troglitazone may have favourable effects on the prevention of CHD in patients with type 2 diabetes, in part through the reduction of the frequency of small, dense LDL particles (48).

ii) Effect of an alpha-glucosidase inhibitor on LDL size

Acarbose, a potent intestinal α-glucosidase inhibitor, reduces the availability of glucose for intestinal absorption and therefore suppresses postprandial plasma glucose and insulin levels in diabetic subjects (49). It has also been reported that postprandial triglyceride levels can be reduced by acarbose treatment (50). Thus, we examined the effect of long-term treatment with acarbose on plasma

![Fig. 6. Changes in LDL size during normal pregnancy and preeclampsia (46).](image)

![Fig. 7. Effect of troglitazone treatment in type 2 diabetic patients on plasma total-triglyceride and LDL size (48).](image)
lipoproteins, especially on RLP fractions and LDL size in type 2 diabetic patients without prominent hyperlipidemia. Twenty-four type 2 diabetic patients (14 on diet control and 10 on sulfonylureas) were examined. Plasma glucose and HbA1c in the total subjects tended to decrease after treatment. Significant suppression was found in HbA1c from the 12th month onward. Cholesterol and triglyceride in total plasma also tended to decrease and the decrease in triglyceride level became significant from the 12th month. There were no significant changes in either apo A1, B, E or HDL-cholesterol during the observation period. Triglyceride concentration in the RLP fraction tended to decrease after treatment and this decrease was significant from the 12th month. However, cholesterol in the RLP fraction showed no significant change after treatment. When the subjects with small sized LDL (less than 25.5 nm in diameter) were examined separately, triglyceride concentrations in both the whole plasma and RLP fraction showed a significant decrease from the ninth month. Their LDL size increased significantly from the 24th month onward. Subjects with normal sized LDL showed no significant change in either total triglyceride or LDL size during the study period. As we already reported (51), acarbose treatment produced a significant decrease in RLP-triglyceride in type 2 diabetic patients, and the precise mechanisms of this are not known. However, it could be that acarbose treatment results in the long-term reduction of monosaccharide availability for the small intestine, thereby contributing to the suppression of intestinal lipid synthesis. It is also noteworthy that acarbose treatment resulted in an enlargement of LDL size in diabetic subjects who had been classified as pattern B with small, dense LDL before treatment. The mechanisms for the production of small, dense LDL are a matter of debate. One proposed mechanism is that the liver in hypertriglyceridemic subjects produces triglyceride-rich VLDL and such particles will become cholesterol-depleted (small, sized) LDL after hydrolysis by peripheral lipase activity. Taken together with the decrease in RLP triglyceride level after acarbose treatment, it is speculated that LDL size can be influenced by the amount and/or composition of intestinal lipoproteins which will thereafter be taken up by the liver. The long-term reduction of monosaccharide availability for the small intestine by acarbose treatment might contribute to the appearance of normal sized LDL through the suppression of intestinal lipid synthesis. Thus, acarbose treatment may have favorable preventive effects on the development of macroangiopathy in diabetic patients through reducing the population of atherogenic lipoproteins such as remnant-like particles and small, dense LDL.

ii) Effect of an alpha1-blocker on LDL size

An alpha1-blocker, doxazosin, has been reported to favorably affect the plasma lipid profile. We examined whether doxazosin could reduce these atherogenic lipoproteins in hypertensive subjects with and without type 2 diabetes (52). Seventeen non-diabetic hypertensive patients and 33 hypertensive patients with type 2 diabetes were studied. Doxazosin (2 to 4 mg) was administered alone or with other previously received antihypertensive drugs for 6 months. Doxazosin effectively decreased blood pressure (BP) without significantly affecting blood glucose, glycosylated hemoglobin (HbA1c), or C-peptide levels in both non-diabetic and diabetic patients. Doxazosin significantly reduced triglyceride, apo CIII, and apo B, but did not alter total-, LDL- or HDL-cholesterol. The mean LDL particle diameter was significantly increased from 25.6 ± 0.6 nm to 25.9 ± 0.4 nm (p < .001) by doxazosin treatment, regardless of the presence of diabetes (Fig. 8). Consequently, the prevalence of small dense LDL (< 25.5 nm) was halved in both groups. The increase in LDL size significantly correlated with a decrease in triglyceride level (r = -.796, p < .0001). Doxazosin significantly reduced RLP-cholesterol in both groups. These results suggest that doxazosin may help to prevent CHD by reducing atherogenic lipoproteins, including small, dense LDL and remnant lipoproteins, in hypertensive patients, regardless of the presence of diabetes.

iv) Effect of fibrates and statins on LDL size

Not only fibrates (53) but also several statins (54) are known to increase LDL size. We examined the effect of fluvastatin on the LDL size and on urine 8-isoPGF2α concentration, a new oxidant stress marker (55, 56), in hyperlipidemic subjects. Fluvastatin administration was successful in increasing the LDL size (from 24.0 ± 0.4 to 25.9 ± 0.3 nm, p < 0.05) and in decreasing urine 8-isoPGF2α concentration (from 2347 ± 713 to 785 ± 98 pg/mg, creatinine, p < 0.05). As already reported, the small, dense LDLs display enhanced susceptibility to copper transition metal-induced oxidation when compared with the normal sized LDL particles (14-16), and it is well known that oxidized LDLs are highly atherogenic (20). Fluvastatin, a new statin with anti-oxidant properties (57), may be favorable for cardiovascular risk management in diabetic patients with hypercholesterolemia.

In conclusion, there is a close relationship between plasma triglyceride and LDL size even at very low levels of plasma triglyceride. A high prevalence of small, dense LDL can be seen in type 2 diabetics (especially with nephropathy) as well as in women with severe obesity. It is noteworthy that more than 76% of Japanese diabetics with CHD had small, dense LDL. Furthermore, young men with high-normal blood pressure have smaller LDL size than those with optimal blood pressure. Finally, decreased LDL particle size can be normalized by a change in lifestyle, and the use of available drugs such as fibrates, statins, and those with the ability to improve insulin resistance.
Fig. 8. Effect of doxazosin on LDL size and the prevalence of small, dense LDL (pattern B) on non-diabetic and diabetic hypertensive patients (52). *:* p < 0.01 and **: p < 0.001 vs pretreatment value. pre: pretreatment of doxazosin, post: 6 months after doxazosin treatment.

References

(3) Austin MA, Hokanson JE, and Brunzell JD: Characterization of low-density lipoprotein subclasses; methodologic approaches and clinical relevance. Curr. Opin. Lipidol., 5: 395-403, 1994


(21) Steinbrecher UP, and Witztum JL: Glucosylation of low-density lipoproteins to an extent comparable to that seen in diabetes slows their catabolism. Diabetes, 33: 130-134, 1984


(40) Kazumi T, A. Kawaguchi A, Sakai K, Hirano T, and Yoshino G: young men with high-normal blood pressure have lower serum adiponectin, smaller LDL
size and elevated heart rate than those with optimal blood pressure. Diabtes Care, 25: 971-976, 2002


(54) Hoogerbrugge N, and Jansen H: Atorvastatin increases low-density lipoprotein size and enhances high-density lipoprotein cholesterol concentration in male, but not in female patients with familial hypercholesterolemia. Atherosclerosis, 146: 167-175, 1999

