Effects of Pitavastatin on Lipoprotein Subfractions and Oxidized Low-density Lipoprotein in Patients with Atherosclerosis*

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Summary: It has been demonstrated that pitavastatin can significantly reduce low-density lipoprotein (LDL) cholesterol (LDL-C), but its impact on lipoprotein subfractions and oxidized low-density lipoprotein (oxLDL) has not been determined. The aim of the present study was to investigate the potential effects of pitavastatin on subfractions of LDL and high-density lipoprotein (HDL) as well as oxLDL in untreated patients with coronary atherosclerosis (AS). Thirty-six subjects were enrolled in this study. Of them, 18 patients with AS were administered pitavastatin 2 mg/day for 8 weeks and 18 healthy subjects without therapy served as controls. The plasma lipid profile, lipoprotein subfractions and circulating oxLDL were determined at baseline and 8 weeks respectively. The results showed that pitavastatin treatment indeed not only decreased LDL-C, total cholesterol (TC), triglycerides (TG) and apolipoprotein B (ApoB) levels, and increased HDL cholesterol (HDL-C), but also reduced the cholesterol concentration of all of the LDL subfractions and the percentage of intermediate and small LDL subfractions. Meanwhile, pitavastatin could decrease plasma oxLDL levels. Furthermore, a more close correlation was found between oxLDL and LDL-C as well as LDL subfractions after pitavastatin treatment. We concluded that a moderate dose of pitavastatin therapy not only decreases LDL-C and oxLDL concentrations but also improves LDL subfractions in patients with AS.
Key words: pitavastatin; atherosclerosis; lipoprotein subfraction; low-density lipoprotein

Dyslipidemia, mainly presented as increased low-density lipoprotein cholesterol (LDL-C), is a very common disorder and has been proven to be closely associated with the development and progress of atherosclerotic cardiovascular disease (ASCVD)[1]. Moreover, a large number of studies have indicated that elevated LDL-C concentration accompanied by lower high-density lipoprotein cholesterol (HDL-C) levels could aggravate the diseased process of ASCVD, resulting in cardiovascular events (CVEs)[2]. However, the use of biomarkers alone such as LDL-C or HDL-C did not provide adequate information regarding the disease development or future events.

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*This work was supported, in part, by Capital Special Foundation of Clinical Application Research (No. Z121107001012015), Capital Health Development Fund (No. 201614035), CAMS Major Collaborative Innovation Project (No. 2016-I2M-1-011) and PUMC Youth Fund (No. 3332018200).

Recently, several studies have indicated that lipoprotein subfractions or particles are more effective for the prediction of development of ASCVD and future CVEs[3–5]. In brief, recent data have strongly suggested that small dense LDL (sdLDL) particle is more atherogenic than large, buoyant ones (lbLDL), and is associated with increased risk of CVD[6, 7]. Moreover, previous observations have showed that oxLDL, an oxidized stress biomarker, plays a critical role in atherogenesis[8, 9], which is associated with the endothelial cell apoptosis and reduced antioxidant capability through the changes of the secretory activities of endothelium[10].

Pitavastatin is a potent, synthetic competitive inhibitor of HMG-CoA reductase (HMGR), which is classified as a moderate- to high-intensity statin that effectively not only reduces LDL-C by 40% in patients with hypercholesterolemia but also provides a sustained increase of HDL-C levels[11]. Moreover, a recent study suggested that administration of highest-dose pitavastatin (4 mg) did not increase the risk of new onset diabetes in patients at high risk of developing diabetes during the 3-year follow-up[12]. A recent meta-

analysis showed that pitavastatin did not adversely affect glucose metabolism or diabetes development compared with placebo or other statins[13]. Therefore, it seems that pitavastatin should preferentially be considered in the treatment of dyslipidemia in more complex patients, for example, diabetic patients or those at risk of developing diabetes. Based on above findings, the aim of the present study was to evaluate the potential effect of pitavastatin on both plasma oxLDL levels and lipoprotein subfractions in humans for the purpose of providing more information with regards to clinical implication of pitavastatin.

1 MATERIALS AND METHODS

1.1 Study Design and Population

The study protocol complied with the Declaration of Helsinki, and was approved by the hospital ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China). All patients gave their informed written consent. The clinical trials registration number is 2013-442. In this present prospective study, 18 patients with angiography-proven atherosclerosis (at least a coronary stenosis lesion more than 50% but less than 70%) in the pitavastatin group were administered pitavastatin at 2 mg/day for 8 weeks. Eighteen healthy subjects who had not received any drug treatment previously were enrolled as the control group. Data regarding serum lipid profile and HDL and LDL subfractions were collected at baseline and at week 8. The inclusion criteria of the present study were as follows: (1) patients with a coronary stenotic lesion between 50%–70% detected by coronary angiography; (2) no treatment history of statins or other drugs known to affect blood lipids; and (3) age 18–70 years. Patients with previous acute coronary syndrome within 1 month, serious heart failure or arrhythmia, infectious disease within 1 month, serious liver or renal dysfunction, autoimmune disease, malignant disease, pregnancy or lactation, or a psychiatric disorder were excluded from the study. In addition, patients with laboratory values > 3-fold the upper limit of normal (ULN) for aspartate aminotransferase or alanine aminotransferase, or > 5-fold the ULN for creatine phosphokinase were also excluded from the study.

1.2 Laboratory Examinations

Blood samples were obtained from the cubital vein at both baseline and 8 weeks after an overnight fasting. All samples were subsequently stored at –80°C and analyzed immediately after thawing. The concentrations of plasma total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, apolipoprotein A-I (ApoA-I) and ApoB were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). Of them, TC, TG, HDL-C and LDL-C levels were measured by enzymatic assay. ApoA-I and apoB levels were measured by turbidimetric immunoassay. Plasma oxLDL levels were detected by a sandwich enzyme-linked immunosorbent assay, according to manufacturer's instructions (Mercodia, Uppsala, Sweden). The detection limit was 0.6 mU/L.

1.3 LDL Subfraction Analysis

The LDL subfractions were also determined electrophoretically using high-resolution 3% polyacrylamide gel tubes and the Lipoprint LDL System (Quantimetrix) as previously described[14]. Seven LDL subfractions were obtained. Subfraction 1 represented large LDL particles; subfraction 2 indicated intermediate LDL particles, and subfractions 3–7 meant small LDL particles. The cholesterol mass (mg/dL) of each LDL subfraction, and the proportion (%) of the cholesterol concentration of LDL subfractions over the TC concentration were subsequently determined.

1.4 HDL Subfraction Analysis

HDL subfraction analysis was performed electrophoretically by the use of high-resolution 3% polyacrylamide gel tubes and the Lipoprint HDL/LDL System (Quantimetrix Corporation, Redondo Beach, USA) according to the manufacturer's instructions as previously described[14, 15]. By this analysis, HDL was divided into 10 subfractions. Subfractions 1–3 represented large HDL particles, subfractions 4–7 indicated intermediate HDL particles, and subfractions 8–10 meant small HDL particles. The cholesterol concentration (mg/dL) of each HDL subfraction and the percentage (%) of the cholesterol concentration of each HDL subfraction over the HDL-C concentration were subsequently determined.

1.5 Statistical Analysis

Data are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. Both Student's *t* test and Mann-Whitney *U* test were used for the comparison of clinical parameters between the two groups. Categorical variables were compared by chi-square test. Differences of the parameters studied between baseline and post-treatment were evaluated by paired samples *t*-test. Statistical significance was defined as $P<0.05$. Statistical analysis was performed with SPSS version 19.0 software (SPSS Inc., USA).

2 RESULTS

2.1 Clinical Characteristics

The baseline clinical characteristics of the study subjects are summarized in table 1. All baseline characteristics were well matched between the two groups.

2.2 Effects of Pitavastatin on the Levels of Lipid Parameters

As shown in table 2, 8-week treatment with 2 mg/day pitavastatin decreased serum levels of TC, TG,

ApoB and LDL-C compared with baseline (P<0.001, P<0.05, P<0.001 and P<0.001, respectively), while increasing HDL-C (P<0.05). Meanwhile, there was no significant change in serum level of ApoA-I after pitavastatin treatment. Not surprisingly, there were no significant changes in any serum lipid parameters in the control group after 8 weeks.

Table 1 Baseline clinical characteristics of the subjects

Variable	Control group (n=18)	Pitavastatin group (n=18)
Demographics		
Age (years)	52.76±8.92	53.94±10.13
Man [n (%)]	8 (44.4)	9 (50.0)
BMI (kg/m^2)	25.21±2.97	24.97±2.89
Clinical profiles [n (%)]		
Family history of CHD	1 (5.6)	1 (5.6)
Smoker	7 (38.9)	8 (44.4)
Hypertension	3 (16.7)	3 (16.7)
Diabetes	2 (11.1)	2 (11.1)
Laboratory values		
ESR (mm/h)	10.17±8.77	11.59±9.66
WBC count (×10^9/L)	6.61±1.53	6.29±1.17
Neutrophils (×10^9/L)	3.63±0.87	3.72±0.94
ALT (U/L)	24.96±11.39	23.11±10.65
AST (U/L)	19.22±7.27	20.78±5.98
Cr (μmol/L)	70.32±11.16	71.92±14.89
BUN (mmol/L)	5.35±1.07	5.64±1.44

Data are expressed as mean ± standard deviation except where stated otherwise. BMI: body mass index; CHD: coronary heart disease; WBC: white blood cell; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; BUN: blood urea nitrogen

2.3 Changes in LDL and HDL Subfractions after Pitavastatin Treatment

The effects of 8-week treatment with 2 mg/day pitavastatin on the cholesterol concentration of LDL and HDL subfractions are summarized in table 2.

There were significant decreases in the concentration of large, intermediate, and small LDL-C (fig. 1B; P<0.01, P<0.001, and P<0.001, respectively), as well as the marked reductions in the percentage of intermediate and small LDL subfractions (fig. 1D; P<0.01 and P<0.001 for both). As was expected, there were no significant differences in the cholesterol levels and the percentage of each LDL subfraction from baseline to the end of the study (8 weeks) in control subjects (fig. 1A and 1C; P>0.05 for both).

However, treatment with 2 mg/day pitavastatin for 8 weeks had no significant impact on either the cholesterol concentration of each HDL subfraction or the percentage of each HDL subfraction (fig. 2B and 2D, P>0.05 for all), while it increased HDL-C concentration (P<0.05). Meanwhile, There were no significant differences in the cholesterol concentration of HDL subfractions between baseline and 8 weeks in the control group (fig. 2A and 2C; P>0.05 for all).

2.4 Changes in OxLDL Levels after Pitavastatin Treatment

The changes in the plasma oxLDL levels in patients following pitavastatin treatment and in control subjects without any therapy are given in table 2 and fig. 3. The data showed that there was no significant change in oxLDL level from baseline to the end of the study

Table 2 Effects of pitavastatin on lipid parameters, lipoprotein subfraction and oxLDL levels

Variable	Control group (n=18)		Pitavastatin group (n=18)	
	Baseline	8 weeks	Baseline	8 weeks
TC (mmol/L)	4.81±1.01	4.86±0.89	5.14±1.02	3.78±0.56***
TG (mmol/L)	1.43±0.85	1.49±0.91	1.68±1.17	1.35±1.04**
ApoA-I (g/L)	1.42±0.31	1.39±0.29	1.37±0.29	1.43±0.31
ApoB (g/L)	1.08±0.19	1.09±0.24	1.16±0.27	0.84±0.20***
LDL-C (mg/dL)	111.39±20.63	112.64±21.39	131.10±35.85	79.26±20.61***
Large LDL-C (mg/dL)	31.54±7.29	31.98±7.17	23.00±9.04	17.22±5.62**
Intermediate LDL-C (mg/dL)	15.16±8.45	15.09±8.31	20.22±7.17	10.72±4.11***
Small LDL-C (mg/dL)	2.63±2.16	2.66±2.39	9.78±6.31	3.22±2.67***
Large LDL (%)	15.97±2.13	15.69±2.89	11.53±3.83	11.64±2.84
Intermediate LDL (%)	7.36±3.84	7.39±4.09	10.04±2.17	7.37±2.49**
Small LDL (%)	1.43±1.19	1.39±1.18	4.99±3.16	2.25±1.86***
HDL-C (mg/dL)	48.57±8.64	47.91±9.07	49.21±9.87	54.75±8.64*
Large HDL-C (mg/dL)	19.72±8.32	19.53±7.69	15.44±6.34	16.83±6.82
Intermediate HDL-C (mg/dL)	20.69±4.65	20.32±5.21	24.83±4.71	26.61±5.62
Small HDL-C (mg/dL)	6.71±2.19	7.01±2.21	9.17±2.60	9.33±2.70
Large HDL (%)	41.19±10.05	40.68±9.78	30.44±8.20	30.98±6.86
Intermediate HDL (%)	43.56±8.71	43.16±7.22	50.67±4.69	50.94±4.23
Small HDL (%)	15.62±4.01	16.37±5.19	18.86±5.49	18.08±5.70
OxLDL (U/L)	53.88±12.45	52.08±9.08	54.13±13.01	36.29±7.91***

Data are expressed as mean ± standard deviation. TC: total cholesterol; TG: triglycerides; ApoA-I: apoprotein AI; ApoB: apoprotein B; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol, $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001 *vs.* baseline (at the same dose).

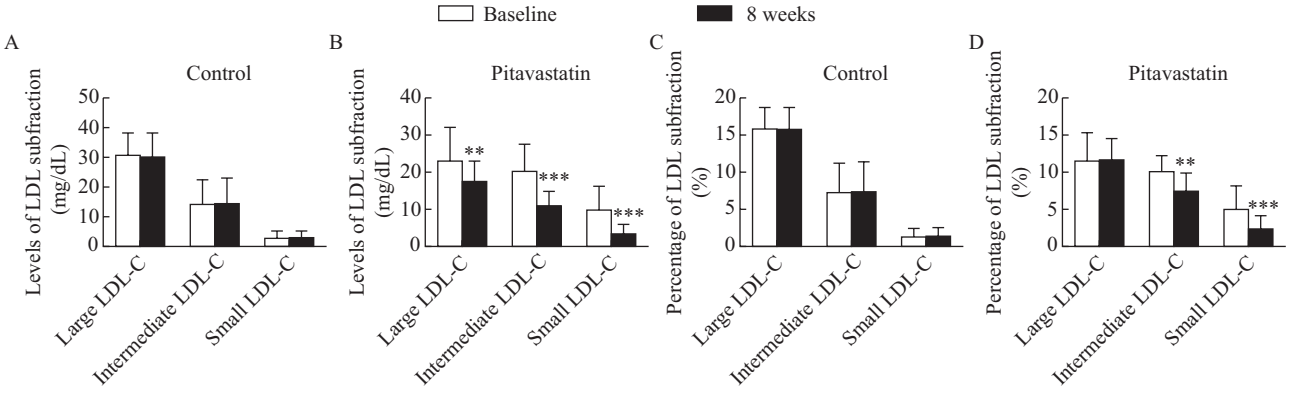

Fig. 1 Effects of pitavastatin on LDL subfractions
There was no significant difference in the cholesterol concentration of each LDL subfraction between baseline and 8 weeks' follow-up in the control group (A) (P>0.05). Pitavastatin treatment for 8 weeks significantly decreased the concentration of large LDL-C, intermediate LDL-C and small LDL-C (B) ($^{**}P$<0.01, $^{***}P$<0.001, respectively). There was no significant difference in the percentage of each LDL subfraction at baseline and 8 weeks in control group (C) (P>0.05). Pitavastatin treatment for 8 weeks significantly decreased the percentage of intermediate LDL-C and small LDL-C (D) (P<0.01 and P<0.001, respectively).

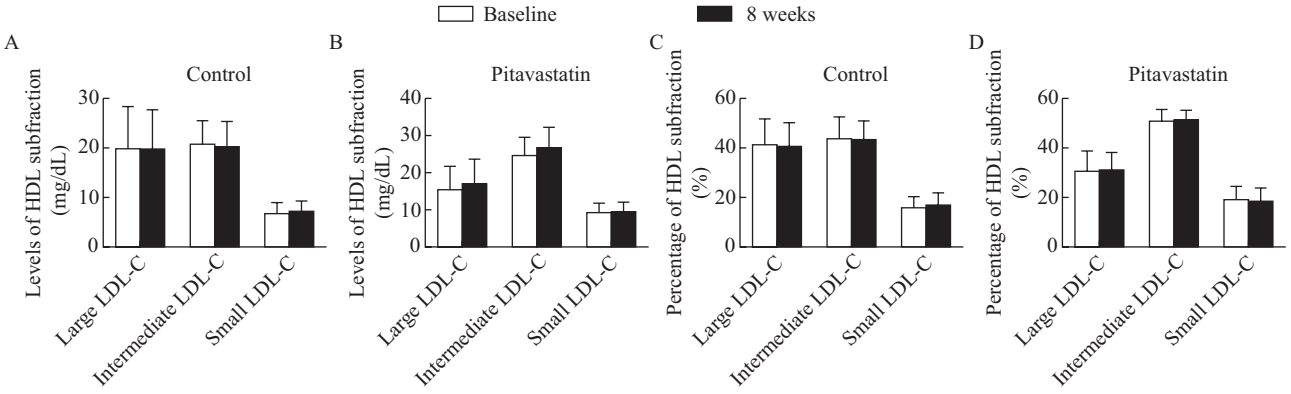

Fig. 2 Effects of pitavastatin on HDL subfractions
There was no significant difference in the cholesterol concentration of each HDL subfraction between baseline and 8 weeks' follow-up both in the control group (A) and pitavastatin group (B) (all P>0.05). There was no significant difference in the percentage of each HDL subfraction at baseline and 8 weeks in control group (C) and Pitavastatin group (D) (all P>0.05).

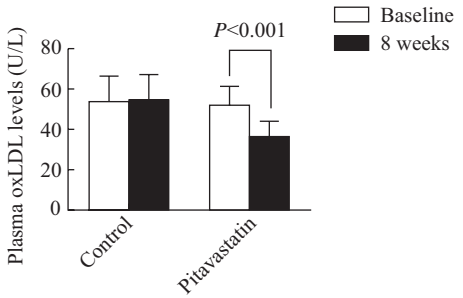

Fig. 3 Effects of pitavastatin on plasma oxLDL levels in patients with atherosclerosis and control subjects
Pitavastatin treatment for 8 weeks significantly decreased oxLDL levels (P<0.001).

(8 weeks) in control subjects. In contrast, there was an obvious decrease in oxLDL levels in patients who received 2 mg/day pitavastatin for 8 weeks (P<0.001).

3 DISCUSSION

It has been confirmed that statins can significantly modify the lipid profile but its impact on subfractons of LDL and HDL has not fully been understood, especially for a relative new statin, pitavastatin. In the present study, the data indicated that treatment with 2 mg/day pitavastatin for 8 weeks could effectively lower plasm LDL-C level, accompanied by the significant change in the LDL subfraction phenotypes. Our data, for the first time, demonstrated that 2 mg/day pitavastatin treatment for 8 weeks could effectively decrease the cholesterol concentration of the LDL subfractions and the percentage of intermediate and small LDL subfractions, as well as reducing plasma oxLDL levels.

Recent studies have shown that increased numbers of LDL particles are associated with increased risk for coronary heart disease (CAD) and more small, dense LDL particles usually have a greater association with CAD[16]. In other words, particle number, rather than LDL cholesterol levels, has been shown to be a better predictor of development of atherosclerotic disease and CVEs[17, 18]. Therefore, assessment of LDL subfractions and LDL particle size has been proposed

as a more reliable method to quantify atherogenicity of the lipoprotein fraction and evaluate the therapeutic efficacy of lipid-lowering drugs[14]. Our previous data demonstrated that 20 mg/day atorvastatin treatment for 8 weeks significantly decreased the cholesterol concentration of the LDL subfractions and mean LDL particle size[19]. A recent study showed that three intensive statins (pitavastatin, atorvastatin, and rosuvastatin) equally improved lipid parameters in patients with hypercholesterolemia, among which 2 mg/day pitavastatin treatment for 16 weeks markedly reduced LDL-C levels and LDL particles[20]. Tokuno *et al* found that 1 mg/day pitavastatin treatment for 12 weeks significantly decreased atherogenic sdLDL particles in type 2 diabetes patients with hypercholesterolemia via the mechanism of decreasing total-LDL[21]. Sone *et al* also found that pitavastatin (2 mg/day for 8 weeks) significantly decreased sdLDL in patients with type 2 diabetes and mixed hyperlipoproteinaemia[22]. In our present study, we demonstrated that 2 mg/day pitavastatin treatment could effectively reduce serum LDL-C levels by decreasing the cholesterol concentration of all LDL subfractions (i.e. large, intermediate and small LDL particles).

Recently, more data confirmed that the quality of HDL particles may be more important than that of HDL[23, 24]. A recent study found an inverse association of large HDL subfraction and a positive association of intermediate and small HDL subfractions with premature CAD[15]. Our previous study also demonstrated that the cholesterol level and the percentage of large HDL subfaction were significantly higher, while the cholesterol level and the percentage of small HDL subfaction were significantly lower in patients with CAD than in healthy subjects, and also showed that both the concentration of small HDL-C and the percentage of small HDL subfraction were independent predictors for the severity of CAD[25]. Kawano *et al* demonstrated that 2 mg/day pitavastatin treatment in hypercholesterolemic patients significantly increased HDL-C levels and remarkably decreased pre-beta1-HDL concentration, while significantly increasing the disappearance rate of pre-beta1-HDL, which suggested that pitavastatin promotes the early step of reversing cholesterol transport[26]. In contrast to their study, we found that 2 mg/day pitavastatin treatment for 8 weeks had no effects on the cholesterol concentration and the percentage of all HDL fractions in patients with atherosclerosis except that HDL-C levels increased. Although the disparities among these studies are unclear, the differences in HDL subclasses measurement, subjects studied, and statin type or dose may be the explanations.

It has been demonstrated that oxLDL is also an independent risk factor for ASCVD[27]. Previous studies suggested a positive impact of statin on oxLDL[28, 29]. Interestingly, Taguchi *et al* found that pitavastatin treatment for 16 weeks significantly decreased plasma malondialdehyde-LDL levels in patients with type 2 diabetes complicated by dyslipidemia[30]. In the present study, our data demonstrated that pitavastatin therapy significantly decreased the plasma oxLDL levels in patients with dyslipidemia, which is useful for the evaluation of oxidative stress in clinical practice. Meanwhile, our study showed that oxLDL was positively associated with LDL-C, intermediate and small LDL subfractions after pitavastatin treatment. Therefore, in addition to lowering the LDL-C levels, pitavastatin may also achieve its anti-atherosclerotic effect by reducing the oxLDL levels and inhibiting oxidative stress, which are shown to be involved in the initiation of atherosclerosis.

There are several limitations to the present study. Firstly, a relatively small sample size from a single center is a limitation but it may be enough to analyze the changes of lipoprotein subfarction and oxLDL following statin therapy. Secondly, the study duration was short, which may not have enabled us to fully uncover the effects of pitavastatin on lipoprotein subfractions. Moreover, the dose-dependent study of pitavastatin on lipoprotein subfraction was not evaluated. Finally, the impact of pitavastatin-induced changes in lipoprotein subfractions and oxLDL on clinical outcome was not investigated because of primary study design.

In summary, the findings of the present prospective study indicated that 8-week therapy with a clinically conventional dose of 2 mg/day pitavastatin could result in significant effects on the concentration of all LDL-C subfractions, the percentage of intermediate and small LDL subfractions in patients with atherosclerosis, as well as the reduction of oxLDL. At the same time, a favorable modification of the HDL subfraction phenotype was found in this study.

Conflict of Interest Statement

No conflict of interests has been disclosured.

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(Received May 7, 2019; accepted Mar. 4, 2020)