Effect of Pitavastatin Treatment on ApoB-48 and Lp-PLA₂ in Patients with Metabolic Syndrome: Substudy of PROspective Comparative Clinical Study Evaluating the Efficacy and Safety of PITavastatin in Patients with Metabolic Syndrome

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Background: Apolipoprotein (Apo) B-48 is an intestinally derived lipoprotein that is expected to be a marker for cardiovascular disease (CVD). Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a vascular-specific inflammatory marker and important risk predictor of CVD. The aim of this study was to explore the effect of pitavastatin treatment and life style modification (LSM) on ApoB-48 and Lp-PLA₂ levels in metabolic syndrome (MS) patients at relatively low risk for CVD, as a sub-analysis of a previous multi-center prospective study.

Methods: We enrolled 75 patients with MS from the PROPIT study and randomized them into two treatment groups: 2 mg pitavastatin daily+intensive LSM or intensive LSM only. We measured the change of lipid profiles, ApoB-48 and Lp-PLA₂ for 48 weeks.

Results: Total cholesterol, low density lipoprotein cholesterol, non-high density lipoprotein cholesterol, and ApoB-100/A1 ratio were significantly improved in the pitavastatin+LSM group compared to the LSM only group (P ≤ 0.001). Pitavastatin+LSM did not change the level of ApoB-48 in subjects overall, but the level of ApoB-48 was significantly lower in the higher mean baseline value group of ApoB-48. The change in Lp-PLA₂ was not significant after intervention in either group after treatment with pitavastatin for 1 year.

Conclusion: Pitavastatin treatment and LSM significantly improved lipid profiles, ApoB-100/A1 ratio, and reduced ApoB-48 levels in the higher mean baseline value group of ApoB-48, but did not significantly alter the Lp-PLA₂ levels.

Keywords: Apolipoprotein B-48; Lp-PLA₂; Metabolic syndrome; Pitavastatin
INTRODUCTION

With an increasing prevalence worldwide, metabolic syndrome (MS) has become a leading health concern [1]. MS is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality [2]. Dyslipidemia is one diagnostic criterion for the MS and these lipid abnormalities are recognized risk factors for cardiovascular disease (CVD) [3]. Statins decrease significant CVD risk in patients with MS by reducing low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels and possibly by decreasing inflammation [4].

Apolipoprotein B (ApoB) is the main structural surface protein found on all β lipoproteins and is known to cause atherosclerosis [5]. Of two type of ApoB, ApoB-48 is an intestinally derived lipid with a chylomicron remnant that increases in postprandial hyperlipidemia, a known risk factor for coronary artery disease (CAD) [6]. The effect of statins on hepatic ApoB-100 is well known [7], but the direct effect of statins on intestinal ApoB-48 is less well understood.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), an emerging biomarker of cardiovascular risk, is an inflammatory enzyme expressed in macrophages of atherosclerotic plaques and carried in the circulation predominantly bound to LDL-C [8,9]. Recently, analysis of data from 32 prospective studies linked LP-PLA2 activity directly with the risk of CVD [10]. Previous studies report that increased Lp-PLA2 activity is associated with MS and incident fatal and non-fatal CVD [11]. High Lp-PLA2 activity is observed in subjects with the MS and associated with several lipid-related risk factors such as ApoB [12].

Therefore, the purpose of the present study was to evaluate the effect of pitavastatin and life style modification (LSM) treatment on ApoB-48 and Lp-PLA2 levels in subjects with MS, using serum samples from the PROPIT (PROspective comparative clinical study evaluating the efficacy and safety of PITavastatin in patients with metabolic syndrome) trial.

METHODS

Trial design

The PROPIT trial was a 12-month, multicenter, prospective, randomized open label study at 10 clinical centers in Korea. The detailed protocol for PROPIT has been previously described [13]. Briefly, after screening, selected subjects with MS were randomized into two groups: the pitavastatin (2 mg daily)+intensive LSM group or the intensive LSM only group. Subjects with LDL ≥190 mg/dL or glycated hemoglobin (HbA1c) ≥8% at the 24-week (6-month) follow-up visit were withdrawn from the study because there was a drug-naïve arm in our study design. All subjects were trained for LSM with the same protocol at the time of enrollment by health professionals.

Study subjects

Between February 2008 and December 2010, 164 MS patients were enrolled in the PROPIT study. Among them, we randomly selected 37 and 38 subjects for the pitavastatin and LSM groups, respectively, after matching for age, sex, and body mass index.

Eligible patients were men and women aged 18 to 75 years with central obesity (waist circumference: men ≥90 cm, women ≥85 cm, according to guideline of the Korean Society for the Study of Obesity) [14] and impaired fasting glucose (fasting glucose ≥100 mg/dL), which are essential components of MS, and one or more of the followings: (1) TG ≥150 mg/dL; (2) high density lipoprotein (HDL) for men ≤40 mg/dL, and for women ≤50 mg/dL; and (3) systolic blood pressure ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mm Hg. Selected subjects had no prior history of atherosclerosis or CVD. They were statin naïve, with no prior use of oral hypoglycemic agents.

The exclusion criteria were the use of statins within the preceding 3 months; uncontrolled hypertension (DBP ≥95 mm Hg); poorly controlled diabetes (HbA1c ≥8.0%); high cholesterolamia (LDL ≥190 mg/dL or TG ≥400 mg/dL); a past medical history of coronary disease, atherosclerosis, malignancy or severe infective disease; renal dysfunction (creatinine ≥2.0 mg/dL) or hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase ≥upper normal limit [UNL] × 2.5); uncontrolled hypothyroidism (thyroid-stimulating hormone ≥UNL × 1.5); creatine phosphokinase ≥UNL × 2; pregnancy or possible pregnancy; and lactation.

Measurement of plasma levels of ApoB-48 and Lp-PLA2

Plasma concentration of ApoB-48 was measured by enzyme-linked immunosorbent assay (ELISA) kit (product code: SEB-883Hu) which is a sandwich enzyme immunoassay for in vitro quantitative measurement of ApoB-48 in human serum, plasma, and other biological fluids. The plasma concentration of Lp-PLA2 was determined by a commercially available Lp-PLA2 ELISA kit (Uscn Life Science Inc., Houston, TX, USA).

Endpoint assessment

The primary end-point was the change from baseline in plasma
level of ApoB-48 and Lp-PLA2: after the 12-month intervention. Secondary end-points included changes from baseline in lipid profiles (TG, HDL, non-HDL, and LDL), ApoB-100/A1 ratio and high molecular weight (HMW) adiponectin.

Statistical analysis
The data are presented as mean±standard deviation for continuous variables and as proportions (%) for categorical variables. Baseline clinical and biochemical characteristics between the two treatment groups were compared using two-sample t test for continuous variables and chi-square test for categorical variables. The changes of the primary end-point and other parameters from baseline within groups were analyzed using a paired t test, and the significance of the changes between the treatment groups were analyzed using a two-sample t test. In a separate analysis, changes from baseline in the levels of ApoB-48 and LpPLA2: according to their baseline values (i.e., below and above median values) were compared using a Wilcoxon signed rank test, and differences in changes between the treatment groups was analyzed using a Mann Whitney U test. All statistical analyses were carried out with SPSS version 21.0 (IBM Co., Armonk, NY, USA). A two-tailed P<0.05 was regarded as statistically significant.

RESULTS

Baseline patient characteristics
All subjects were patients with MS, obesity and prediabetes, and all were statin naïve, with no prior use of oral hypoglycemic agents. The two groups of patients were well-matched according to lipid profile, blood glucose level and the pattern of life style including the frequency of exercise, alcohol consumption and smoking. The mean body mass index and fasting plasma glucose level were around 27 kg/m² and 115 mg/dL, respectively. The number of subjects with coronary heart disease family history, insulin resistance (homeostasis model assessment of insulin resistance), and inflammation state (high-sensitivity C-reactive protein) did not differ between groups. Baseline characteristics of the study subjects are summarized in Table 1.

Changes in metabolic parameters, apolipoprotein, and Lp-PLA2: in both groups after 12 months of treatment
After the 12 months of treatment, LDL-C and non-HDL cholesterol (HDL-C) were significantly reduced in the pitavastatin +LSM group compared with those in the LSM only group (Table 2). TG level was significantly lower in the pitavastatin +LSM group but slightly higher in LSM only group, but the differences were not significant (TG change: –24.7±54.1 mg/dL vs. 2.7±98.1 mg/dL, P=0.143).

The ApoB-100/A1 ratio was also significantly lower in both groups, but was much greater in the pitavastatin+LSM group (ApoB-100/A1 ratio change: –0.21±0.16 vs. –0.05±0.12, P<0.001).

HMW adiponectin increased in both groups, but there was no significant difference between the two groups. We evaluated the

### Table 1. Baseline Characteristics of Subjects in the Sub-Analyses

| Variable                        | Pitavastatin+LSM (n=37) | Only LSM (n=38) | P value |
|---------------------------------|-------------------------|-----------------|---------|
| Age, yr                         | 52.9±8.5                | 52.0±9.1        | NS*     |
| Male sex                        | 22 (59.5)               | 25 (65.8)       | NS*     |
| BMI, kg/m²                      | 26.8±2.2                | 27.1±3.6        | NS*     |
| WC, cm                          | 91.8±4.4                | 94.3±6.5        | NS*     |
| SBP, mm Hg                      | 129.6±10.1              | 126.3±11.1      | NS*     |
| DBP, mm Hg                      | 80.7±6.6                | 80.8±7.3        | NS*     |
| Exercise, time/wk               |                         |                 |         |
| ≥3                              | 15 (40.5)               | 18 (47.4)       | NS*     |
| 1–3                             | 10 (27.0)               | 6 (15.8)        |         |
| Never                           | 12 (32.4)               | 14 (36.8)       |         |
| Current smoker                  | 10 (27.0)               | 12 (31.6)       | NS*     |
| Alcohol habits, time/wk         |                         |                 |         |
| ≥3                              | 14 (37.8)               | 17 (44.7)       |         |
| <3                              | 14 (37.8)               | 11 (28.9)       |         |
| Never                           | 9 (24.3)                | 10 (26.3)       |         |
| CHD family history              | 9 (24.3)                | 9 (23.7)        | NS*     |
| FPG, mg/dL                      | 114.1±11.1              | 116.5±14.9      | NS*     |
| Total cholesterol, mg/dL        | 223.6±28.7              | 215.5±26.5      | NS*     |
| HDL-C, mg/dL                    | 49.2±9.6                | 46.9±10.0       | NS*     |
| LDL-C, mg/dL                    | 144.7±19.8              | 136.1±24.0      | NS*     |
| Non-HDL-C, mg/dL                | 174.4±28.8              | 168.6±24.4      | NS*     |
| TG, mg/dL                       | 162.4±50.6              | 175.8±72.9      | NS*     |
| hs-CRP, mg/dL                   | 0.15±0.16               | 0.19±0.32       | NS*     |
| HOMA-IR                         | 2.9±1.2                 | 3.5±1.7         | NS*     |

Values are expressed as mean±SD or number (%). LSM, life style modification; NS, not significant; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.

*The P values are computed from two-sample t test; bThe P values are computed from v2-test.
Pitavastatin and ApoB48

Table 2. Changes of Metabolic Parameters after 12 Months Intervention in Both Groups

| Variable          | Pitavastatin+LSM (n=37) | LSM only (n=38) | P value* |
|-------------------|--------------------------|----------------|---------|
|                   | Baseline     | 12 months   | Change   | Baseline     | 12 months   | Change   |         |
| TC, mg/dL         | 223.6±28.7  | 178.2±25.9  | −45.4±34.7  | 215.7±26.8  | 215.7±22.7  | 0±22.5   | <0.001  |
| TG, mg/dL         | 162.4±50.6  | 137.7±54.2  | −24.7±54.1  | 175.8±72.9  | 179.6±106.6 | 2.7±98.1 | NS      |
| HDL-C, mg/dL      | 49.2±9.6    | 49.9±9.0    | 0.7±6.2    | 47.2±10.0   | 49.2±8.5    | 2.0±7.3  | NS      |
| LDL-C, mg/dL      | 144.7±19.8  | 103.0±24.5  | −41.7±29.6  | 135.8±24.3  | 134.1±22.3  | −1.7±23.2 | <0.001  |
| Non-HDL-C, mg/dL  | 174.4±28.8  | 138.4±28.7  | −46.0±34.4  | 168.6±24.4  | 166.5±22.8  | −2.0±21.2 | <0.001  |
| ApoB-100/A1 ratio | 0.75±0.17   | 0.55±0.18   | −0.21±0.16  | 0.71±0.18   | 0.66±0.13   | −0.05±0.12 | <0.001  |
| Adiponectin, μg/mL| 2.40±0.997  | 3.37±1.47   | 0.965±1.38  | 3.15±1.87   | 3.67±1.76   | 0.519±1.14 | NS      |
| HMW-adiponectin, μg/mL | 2.20±1.30 | 2.61±1.70   | 0.404±1.01  | 2.20±1.30   | 3.06±2.77   | 0.775±1.07 | NS      |
| ApoB-48, μg/mL    | 5.64±1.55   | 5.36±1.75   | −0.272±2.17 | 5.98±3.20   | 6.36±2.62   | 0.382±4.05 | NS      |
| Lp-PLA₂, μg/mL    | 1.20±0.262  | 1.25±0.251  | 0.048±0.225 | 1.21±0.241  | 1.33±0.316  | 0.116±0.288 | NS      |

Values are expressed as mean±SD.

LSM, life style modification; TC, total cholesterol; TG, triglyceride; NS, not significant; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ApoB-100, apolipoprotein B100; ApoA1, apolipoprotein A1; HMW, high molecular weight; Lp-PLA₂, lipoprotein-associated phospholipase A₂.

Comparison of the changes between the groups by two-sample t test; tP<0.05 by paired t test.

Table 3. Changes from Baseline in the Levels of ApoB-48 and Lp-PLA₂ according to Their Baseline Values (i.e., Below and Above Median Values)

| Variable          | Pitavastatin+LSM (n=37) | LSM only (n=38) | P value* |
|-------------------|--------------------------|----------------|---------|
|                   | Baseline     | 12 months   | Change   | Baseline     | 12 months   | Change   |         |
| Below median, μg/mL|             |             |          |             |             |          |         |
| ApoB-48           | 4.54 (4.02–4.89) | 4.64 (3.83–6.35) | 0.15 (−0.65 to 2.09) | 4.57 (4.11–4.94) | 5.46 (4.70–6.11) | 0.68 (0.21–1.70) | 0.234 |
| Lp-PLA₂           | 1.02 (0.86–1.17) | 1.12 (0.94–1.38) | 0.16 (0.00–0.30) | 1.02 (0.91–1.11) | 1.22 (1.14–1.30) | 0.19 (0.10–0.33) | 0.331 |
| Above median, μg/mL|             |             |          |             |             |          |         |
| ApoB-48           | 6.09 (5.62–7.30) | 5.07 (4.67–5.75) | −0.88 (−2.51 to −0.65) | 6.41 (5.64–7.70) | 5.99 (5.11–6.63) | 0.14 (−1.69 to 0.67) | 0.045 |
| Lp-PLA₂           | 1.44 (1.27–1.48) | 1.40 (1.27–1.56) | −0.03 (−0.15 to 0.11) | 1.34 (1.29–1.44) | 1.44 (1.15–1.54) | 0.06 (−0.18 to 0.15) | 0.598 |

Values are expressed as median (interquartile range). The values corresponding to the median of baseline apoB-48 and Lp-PLA₂ are 5.42 and 1.23 μg/mL, respectively.

ApoB-48, apolipoprotein B48; Lp-PLA₂, lipoprotein-associated phospholipase A₂; LSM, life style modification.

Comparison of the changes between the groups by Mann-Whitney U test; tP<0.05 by Wilcoxon signed rank test.

change of Lp-PLA₂ and ApoB-48 levels before and after intervention. Pitavastatin+LSM did not significantly affect ApoB-48 levels in subjects overall, but when we evaluated changes from baseline in ApoB-48 level according to baseline values (i.e., below and above median values), pitavastatin+LSM significantly reduced ApoB-48 levels in the group with above median baseline value of ApoB-48. There was no effect of pitavastatin+LSM on Lp-PLA₂ in either group (Table 3).

DISCUSSION

We conducted a sub-analysis of the PROPIT study to evaluate the effect of combined therapy with a statin and LSM on lipid profiles, ApoB-48 and Lp-PLA₂ in MS patients. In our study, pitavastatin treatment significantly improved lipid profiles and reduced ApoB-48 levels in the higher mean baseline value group of ApoB-48, but did not significantly alter the Lp-PLA₂ levels.

Insulin resistance is a major component of MS and represents major complications associated with atherogenic dyslipidemia [15]. Atherogenic dyslipidemia in MS patients is characterized by low HDL-C and high TG levels. TGs are associated with TG-rich lipoproteins (TRLs), and chylomicron remnants have been implicated as significant risk factors for atherosclerosis.
The small intestine regulates lipid metabolism in fed and fasting states and plays a central role in lipid homeostasis [6,16]. Since the small intestine consists of insulin sensitive tissue, lipid synthesis pathways in the small intestine are also influenced by insulin resistance. ApoB-48 is present only in intestinally derived lipoproteins such as chylomicron and chylomicron remnants. High ApoB-48 levels suggest delayed metabolism of TRLs, which are commonly associated with insulin resistance and abdominal obesity [19]. In our study, we measured Lp-PLA activity. Winkler et al. [31] reported that 80 mg/day of fluvastatin for 8 weeks decreased the activity of Lp-PLA by 22.8% in subjects with type 2 diabetes. Schaefer et al. [32] also reported that 40 mg/day of atorvastatin reduced mean Lp-PLA values by 26% over 36 weeks in 84 patients who had coronary heart disease and LDL-C levels >130 mg/dL. In contrast to previous studies, pitavastatin (2 mg/day) treatment did not reduce Lp-PLA levels in our study.

There were some differences between our study and previous studies in Lp-PLA activity. Previously, the effect of statins on Lp-PLA activity in subjects at high risk for CVD due to previous coronary disease or diabetes mellitus. However, this study excluded subjects at high risk for CVD (uncontrolled hypertension [DBP ≥95], poorly controlled diabetes [HbA1c ≥8.0%), or high cholesterol levels [LDL ≥190 mg/dL or TG ≥400 mg/dL]). Possibly because we focused on patients at relatively low risk for CVD, the effect of pitavastatin on the change of Lp-PLA was lower than in previous studies. Another difference compared to other studies was the dosage of statin. Pitavastatin 2 mg shows similar effects to atorvastatin 10 mg in improving lipid profiles [33]. Prior studies investigating the effect of statins on the level of Lp-PLA used a higher dosage of statin sufficient to reduce the level of Lp-PLA. We thought that the dosage of pitavastatin in present study was not enough to change the levels of Lp-PLA. In addition, we measured the mass concentration of Lp-PLA by commercial assay. The median value of Lp-PLA has varied widely in prior epidemiologic studies, making it difficult to use this assay for clinical purposes. It has been suggested that a measure of Lp-PLA activity might serve as a more reproducible and representative biomarker of enzyme functions [34]. If we measured Lp-PLA activity with Lp-PLA mass concentration, we would have more accurate results for the effect of pitavastatin on Lp-PLA.

Some important limitations of this study deserve mention. First, it was a sub-study with a relatively small number of subjects. Accordingly, the plasma levels of ApoB-48 and Lp-PLA had wide standard deviations and statistical power was reduced. The strength of this study was that it is the first inter-
ventional study that investigated the effect of pitavastatin on the level of ApoB-48 and Lp-PLA₂.

In conclusion, pitavastatin+LSM in MS patients at relatively low risk for CVD significantly reduced ApoB-48 levels in the higher baseline mean value group of ApoB-48, but did not significantly alter Lp-PLA₂ levels. Further studies with modified dosage and larger populations are needed to evaluate the effects of pitavastatin treatment on Lp-PLA₂ and ApoB-48.

CONFLICTS OF INTEREST

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