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Effects of change in high-density lipoprotein cholesterol by statin switching on glucose metabolism and renal function in hypercholesterolemia

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BACKGROUND: Recent reports have suggested that high-density lipoprotein (HDL) is metabolically related to glucose metabolism and renal function. Statin administration clinically increases HDL cholesterol (HDL-C).

OBJECTIVE: To confirm that change in HDL-C by statin switching is associated with glucose metabolism and renal function in hypercholesterolemic patients.

METHODS: In hypercholesterolemic outpatients (n = 129) who had taken either statin, as atorvastatin, pitavastatin, or rosuvastatin and switched to another statin, the relationship of change in HDL-C to glycated hemoglobin and estimated glomerular filtration rate (eGFR) was assessed.

RESULTS: Change in HDL-C did not significantly correlate with change in HbA1c, eGFR calculated from creatinine (eGFRcre), and eGFR calculated from cystatin C (eGFRcys). The subjects were then divided into 2 groups by change in HDL-C: no change or decrease in HDL-C (HD group) and increase in HDL-C (HI group). In the HI group, apolipoprotein A-1 (Apo A-1) and eGFRs were significantly increased by statin switching. There were significant differences in changes in HDL-C, Apo A-1, lipoprotein lipase, glycated hemoglobin, and eGFR calculated from creatinine between the groups. In the patients with impaired glucose tolerance or diabetes, change in HbA1c was also significant between the groups.

CONCLUSIONS: Our data suggest that an increase in HDL-C due to statin switching is associated with improvement in glucose metabolism and renal function.

Introduction

High-density lipoprotein (HDL) plays a major role in reverse cholesterol transport and also has antiatherogenic properties, including antioxidative stress, anti-inflammation, and improvement of endothelial function.[1–3] A low level of

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HDL cholesterol (HDL-C) is a strong risk factor for cardiovascular disease,[4–6] in spite of a low level of low-density lipoprotein cholesterol (LDL-C).

Statins, LDL-C–lowering agents, reduce the incidence of cardiovascular events. Despite their use, residual cardiovascular risk still remains with a low level of HDL-C.[7–9]

Recent reports have suggested that HDL and apolipoprotein A-1 (Apo A-1) are related to glucose metabolism and renal function.

HDL and Apo A-1 stimulate insulin secretion by interaction with ATP-binding cassette sub-family A member 1 (ABCA1), ATP-binding cassette sub-family G member 1 (ABCG1), or scavenger receptor class B type I (SR-BI) and also inhibit apoptosis of pancreatic beta cells (β-cells).[10] In multivariate analyses of the GREek Atorvastatin and Coronary heart disease Evaluation study[11] and LIvalo Effectiveness and Safety study,[12] change in HDL-C was identified as a significant factor in increasing estimated glomerular filtration rate (eGFR) during statin treatment.

Besides preventing cardiovascular disease, HDL is associated with glucose metabolism and renal function. Although statin administration is one of the medical treatment strategies for elevating HDL-C, there have been few reports that have investigated the relationship between change in HDL-C by statin switching and glucose homeostasis and renal function in hypercholesterolemic patients who take statins.

We previously compared the effect on residual risk factors of 3 statins (atorvastatin [ATO], pitavastatin [PIT], and rosuvastatin [ROS]) by statin switching and reported that the effects on HDL-C and Apo A-1 were significantly different between the statins.[13] In this report, PIT had a favorable effect on the level of HDL-C and Apo A-1 compared with other statins. In the present report, using the data of a previous study,[13] we analyzed whether an increase in HDL-C by statin switching ameliorates glucose homeostasis and renal function.

Methods

Study design and data collection

The present study is a subanalysis of a previous report, a prospective, open-labeled, multicenter study performed at 4 clinics in Ishikawa, Japan, that evaluated the effects of 3 statins on cardiovascular residual risks.[13] Patients were recruited between June 2010 and October 2010. Eligible patients were men and women aged 20 years or older who were administrated 10-mg/d ATO, 2-mg/d PIT, or 2.5-mg/d ROS, which are regular dose in Japanese practice and have comparable effect on LDL-C lowering, for at least 6 months. Major exclusion criteria were type III hyperlipidemia, secondary hyperlipidemia, severe renal or liver impairment or dysfunction, and type I diabetes mellitus. After informed consent was obtained, eligible patients were switched to another statin at the discretion of the physicians without any washout period. The study protocol was approved by the Research Ethics Committee of Kanazawa Medical University. Of the 136 eligible patients enrolled, 7 refused to allow publication of their data. Of the 129 enrolled outpatients, 40 subjects receiving ATO switched to PIT (n = 19) or ROS (n = 21), 39 subjects receiving PIT switched to ATO (n = 19) or ROS (n = 20), and 50 subjects receiving ROS switched to ATO (n = 20) or PIT (n = 30). The laboratory values before and 3 months after switching were measured in nonfasting serum. In the present analysis, the relationship between change in HDL-C and change in glucose metabolism and renal function is investigated.

Measurements and calculations

Nonfasting blood was collected before and 3 months after switching statins. Serum and plasma were separated and stored at each clinic, then measured by an external laboratory (ALP, Kanazawa, Ishikawa, Japan). Total cholesterol, direct method LDL-C, HDL-C, triglyceride, remnant-like lipoprotein particles cholesterol, malondialdehyde-modified LDL, Apo A-1, Apo B, Apo E, preheparin lipoprotein lipase (LPL) mass, glycated hemoglobin (HbA1c), serum creatinine, and cystatin C were measured.

Serum cystatin C has also been used to assess renal function and serum creatinine.[14] In the recent report, cystatin C is superior in predicting GFR to creatinine in Japanese subjects with normal and mildly reduced GFR.[15]

HDL-C was evaluated as an HDL-related factor. HbA1c was evaluated as a glucose homeostasis–related factor, and eGFRs calculated by creatinine and cystatin C were evaluated as a renal function–related factor. eGFR calculated by creatinine (eGFRcre) was assessed using the standard Japanese equation[16]:

$$\begin{aligned}\mathrm{eGFRcre}\left(\mathrm{mL/min/1.73m^2}\right) = {} & 194 \times (\mathrm{serum\,creatinine})^{-1.094} \\ & \times (\mathrm{Age})^{-0.287} \\ & \times (0.739, \mathrm{if\,female})\end{aligned}$$

eGFR calculated by cystatin C (eGFRcys) was assessed using following equation[15]:

$$\begin{aligned}\mathrm{eGFRcys}\left(\mathrm{mL/min/1.73m^2}\right) = {} & 104 \times (\mathrm{serum\,cystatin\,C})^{-1.019} \\ & \times 0.996^{-(\mathrm{age})} \\ & \times (0.929, \mathrm{if\,female}) - 8\end{aligned}$$

Statistical analysis

Data are expressed as mean ± standard deviation. Student *t* test or chi-squared test was used where appropriate. Statistical tests were 2-sided with a 5% significance level.