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Changes in high-density-lipoprotein cholesterol upon statin treatment in type 2 diabetic patients: A meta-analysis

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Abstract *Background and aim:* To investigate the diversity of change in high-density-lipoprote in cholesterol (HDL-C) after statin treatment in patients with type 2 diabetes mellitus (T2DM).
Methods and results: A systemic review searched for trials that reported a serum change in HDL-C in patients with T2DM after statin treatment, and extracted data for meta-analysis. Of 6709 articles surveyed, 160 articles were identified as eligible articles. In the analysis of simvastatin, serum HDL-C was increased in Non-Asian and Asian patients with T2DM by 2.17 mg/dl (95% CI 1.43 ~ 2.90 mg/dl, $p < 0.001$) and 2.31 mg/dl (95% CI 1.37 ~ 3.25 mg/dl, $p < 0.001$), respectively. In the analysis of atorvastatin, although significant, serum HDL-C was subtly increased in Non-Asian patients with T2DM by 1.14 mg/dl (95% CI 0.28 ~ 2.01 mg/dl, $p = 0.010$) mg/dl; however, atorvastatin treatment did not significantly change the serum HDL-C by 0.12 mg/dl (95% CI −1.04 ~ 1.27 mg/dl, $p = 0.839$) mg/dl in Asian patients with T2DM. According to meta-regression analysis, the baseline HDL-C did not affect the change in serum HDL-C in Asian patients with T2DM after either simvastatin or atorvastatin treatment. However, contrary to simvastatin, the coefficient of regression (r) showed a significant negative association ($r = -0.18$; 95% CI −0.32 to −0.04; $p = 0.01$) between baseline HDL-C and the change of HDL-C in non-Asian patients with T2DM after atorvastatin treatment.
Conclusion: We have demonstrated for the first time that there may be a discrepancy in the change of serum HDL-C in Asian patients with T2DM after atorvastatin treatment.

Introduction

Statins have been widely prescribed for cardiovascular diseases (CVDs) prevention based on cumulative evidence from statin trials; however, the relative risk reduction achieved with statins has been reported to be approximately 20 ~ 40%, meaning that 60 ~ 80% of CVD events are not prevented [1]. Consequently, the cardiovascular risk among statin-treated individuals remains high and has been termed "residual risk". Among the possible residual risk factors, high-density lipoprotein cholesterol (HDL-C) has a place in contributing to CVDs [2].

The association between HDL-C and CVDs was first recognized in the 1970s [3]. In the Framingham study, HDL-C was the primary factor accounting for coronary heart disease, and this connection persisted even after adjustment of other lipid parameters [3]. Likewise, according to the United Kingdom Prospective Diabetes Study, the total cholesterol to HDL-C ratio was also valued as an

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important indicator for prediction of the future incidence of coronary heart disease and stroke in type 2 diabetic patients [4,5]. Additionally, studies have indicated that HDL-C remains a risk modifier for CVDs in patients under statin treatment [6,7], even among patients with LDL-C levels reduced to below 70 mg/dl by atorvastatin treatment [8]. In association with our recent results, it has been demonstrated that serum HDL-C is a marker of diabetic nephropathy [9], and these reports outlined that the importance of serum HDL-C change after statin treatment should not be overlooked.

The belief that "statins treatment is of benefit in raising serum HDL-C" may require reassessment in type 2 diabetic patients. In the ASCOT-LLA study, the serum HDL-C level did not increase in diabetic patients after statin treatment [10]. In contrast, in the CARDS study, the serum HDL-C level had reduced by approximately 9% in diabetic patients by the end of study [11]. Recently, in our 1-year follow-up of 1080 participants, we found that Chinese type 2 diabetic patients did not exhibit an increase in HDL-C after atorvastatin or simvastatin treatment [12]. In light of the fact that inter-ethnic differences exist in the drug response to statins, particularly in those of Asian descent [13], the present study was performed (1) to review the literature to verify the different responses of HDL-C to statin therapy in type 2 diabetic patients, and (2) to assess whether ethnicity (i.e., Asian vs. non-Asian) plays a role in this response.

Methods

This report followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements when feasible.

Data source and searches

A systematic review of the available literature to the end of Jan.2014 was performed in the PubMed, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) databases by two independent investigators (Y-H Chang, K-D Lin). We used a combination of "statin" and "diabetes" to find relevant articles.

Study selection

To obtain a comprehensive overview of serum HDL-C change after statin treatment, studies were selected if the study reported the serum HDL-C concentration before and after statin treatment, regardless of the study design or underlying comorbidities of the study participants. However, an eligible study was required to have a statin treatment period of at least 4 weeks for a steady therapeutic effect. In addition, for cross-over design studies, a washout period of 4 weeks was necessary for inclusion. Articles were excluded based on the following criteria: (1) review articles, letters and meeting abstracts; (2) participants included non-diabetic patients or studies of type 1 diabetes mellitus; (3) cerivastatin, which was withdrawn from market, as the investigated drug; (4) unavailable data regarding the change of HDL-C from baseline to the end of follow-up; (5) duplicate studies and studies that extended an original study; (6) non-English articles. To resolve discrepancies, consensus was reached with other specialists (S-J Shin, Y-J Lee) who were not involved in the initial search procedure.

Data synthesis and analysis

Data extraction was conducted independently by 2 authors (Y-H Chang, K-D Lin) using a standardized data extraction form. We extracted the mean and standard deviation (SD) values of pre-/post-statin HDL-C concentration or of HDL-C differences after statin therapy. If a study provided medians (interquartile ranges), we converted them to means (SD) as described by Hozo and colleagues [14]. For reports that lacked the SD, this was estimated from the pooled results of the SD values of included studies [15]. For studies that reported more than one serum HDL-C level after statin treatment, we extracted the last value reported in the trial. To calculate the sampling variance, pre-/post-test scores correlation was needed. For the reason that most of the included studies did not report this, a common value of 0.5 was assumed. In order to check whether the value of the correlation coefficient affected the meta-analytic results, sensitivity analysis was carried out, which consisted of calculation of the sampling variances of the effect sizes by assuming r values of 0.2 and 0.8. Differences in means (mg/dl) and 95% confidence intervals (95% CI) were used as the main effect size of the statin effects on HDL-C change. The following data were extracted from eligible studies: name of first author, publication year, characteristics of participants (i.e., age, A1c, body mass index), generic name of statin and dose, study period, baseline lipid level (i.e., HDL-C, LDL-C and triglycerides) and country in which the study was conducted. With regard to the ethnicity information, we assumed a classification of "Asian" if the study conducted was in an Asian country with a homogeneous population (e.g., China, Japan, Korea and Taiwan).

In the meta-analysis graphical representation, the area of the black square indicates the weight contributed by each individual population. We estimated the between-study heterogeneity using the Cochran Q statistic. Substantial heterogeneity was considered when $p < 0.1$, which was deemed to be a sensible cut-off value [16]. We used the random-effect model if heterogeneity was observed, while the fixed-effect model was applied in the absence of heterogeneity. We performed a meta-analysis including all of the eligible studies followed by a subgroup analysis predefined according to the ethnicity of the diabetic patients. We also performed sensitivity analyses by omitting one study at a time and calculating the pooled differences in means for the remainder of the studies. Publication bias was assessed by Egger's test. Maximum likelihood meta-regression analysis was used to test significant factors in the change of serum HDL-C. All analyses were performed using Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, http://www.meta-analysis.com). We