Editorial

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Combining Ezetimibe and Rosuvastatin: Impacts on Insulin Sensitivity and Vascular Inflammation in Patients with Type 2 Diabetes Mellitus

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Statins, inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase, have been proven effective in reducing cholesterol levels and in decreasing the risk of cardiovascular events in both primary and secondary prevention contexts [1]. However, even with statin therapy, patients with type 2 diabetes mellitus (T2DM) continue to face a significant risk of cardiovascular events, highlighting the necessity for additional lipid-modifying approaches to meet this issue [2]. Ezetimibe, an inhibitor of the Niemann-Pick C1-like 1 (NPC1L1) protein, impedes absorption of cholesterol in the intestines, lowering circulating cholesterol level through a mechanism different from that employed by statins [3]. Adding ezetimibe to a certain dose of statin has been shown to enhance cardiovascular outcomes in adults who recently suffered acute coronary syndrome. Notably, in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), combining simvastatin (40 mg) with ezetimibe led to a further decrease in low-density lipoprotein cholesterol (LDL-C) level and better cardiovascular outcomes compared to simvastatin (40 mg) with placebo in adults age 50 years and older who had experienced acute coronary syndrome in the previous 10 days [4]. These results support the recommendations from current dyslipidemia management guidelines suggesting ezetimibe as an effective non-statin treatment option for high-risk patients with T2DM and established atherosclerotic cardiovascular disease [5,6].

Notably, in a subgroup analysis of the IMPROVE-IT trial, the combination of ezetimibe with statins resulted in a marked improvement in cardiovascular outcomes, especially among patients with T2DM [4]. In patients with T2DM, simvastatin/ezetimibe combination therapy led to a 5.5% decrease in the 7-year Kaplan-Meier primary endpoint event rate. The most notable relative decreases were observed in myocardial infarction (MI) at 24% and ischemic stroke at 39%. For patients without T2DM but with a high cardiovascular risk score, simvastatin/ezetimibe combination therapy resulted in a notable 18% relative decrease in the combined occurrences of cardiovascular death, MI, and ischemic stroke compared to simvastatin monotherapy. A retrospective cohort study from Korea found that simvastatin/ezetimibe combination therapy was linked to a reduced rate of major adverse cardiovascular events (MACE) compared with simvastatin monotherapy and was more effective in individuals with T2DM than in those without T2DM [7]. Moreover, a meta-analysis encompassing seven randomized clinical trials (RCTs) revealed that a combination of statins and ezetimibe reduced the incidence of MACEs more effectively than statins alone, especially in patients with T2DM compared to those without T2DM [8]. In another large, placebo-controlled study that assessed the effectiveness of simvastatin/ezetimibe combination versus simvastatin alone in reducing cardiovascular events in patients with chronic kidney disease, similar preferential effects of the combination therapy were noted in patients with T2DM [9].

Han et al. [10] aimed to compare the effects of rosuvastatin monotherapy and rosuvastatin/ezetimibe combination therapy

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on the lipid profile, insulin sensitivity, and vascular inflammatory response in patients with T2DM. Among 101 patients with T2DM and dyslipidemia, participants were randomly assigned to two treatment groups: one receiving rosuvastatin monotherapy (5 mg/day, $n=51$) and the other undergoing a combination therapy of rosuvastatin and ezetimibe (5 mg/10 mg/day, $n=50$). During the 12 weeks of treatment, LDL-C level declined significantly in both groups. The change was −47.60±30.38 mg/dL (−33.78%±19.92%) in the rosuvastatin group and −69.38±25.46 mg/dL (−50.86%±16.51%) in the rosuvastatin/ezetimibe group, a significant difference ($P<0.001$). About 19% of patients in the rosuvastatin group and 62% of patients in the rosuvastatin/ezetimibe group showed an at least 50% reduction in LDL-C level after 12 weeks of treatment. Additionally, serum triglyceride level decreased in both groups following treatment.

The authors also evaluated the changes in the homeostasis model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, as well as alterations in the levels of serum peroxiredoxin 4 (PRDX4), an antioxidative protein, and serum soluble intercellular adhesion molecule-1 (sICAM-1), an indicator of endothelial activation, following the 12-week treatment period [10]. Based on percentage decrease in LDL-C level after treatment, a significant decrease in HOMA-IR level ($P=0.001$) and a significant increase in serum PRDX4 level ($P=0.002$) were observed only in the subgroup with a ≥50% reduction in LDL-C level in the rosuvastatin/ezetimibe group. No such difference was noted in the subgroup treated with rosuvastatin monotherapy. However, the changes in HOMA-IR and PRDX4 were not significantly different between the two groups after adjusting for diabetes duration and hypertension. Serum level of sICAM-1 increased in both treatment groups, and the extent of change in serum sICAM-1 level was comparable between the two groups ($P=0.232$). This study indicated that, while the rosuvastatin/ezetimibe combination therapy was more effective in reducing LDL-C level than rosuvastatin monotherapy, it did not provide additional benefits in terms of enhancing insulin sensitivity or mitigating vascular inflammatory responses.

Several potential biological mechanisms have been suggested to explain the positive outcomes of combined ezetimibe and statins in individuals with T2DM. Patients with T2DM have been shown to exhibit a notable increase in the expression of NPC1L1 mRNA in the duodenum compared to those without T2DM [11]. Moreover, a significant association has been established between chylomicron cholesterol level and NPC1L1 mRNA expression in patients with T2DM [11]. Given that the NPC1L1 protein is the recognized target of ezetimibe therapy, the elevated level of NPC1L1 observed in patients with T2DM indicate that they might particularly benefit from addition of ezetimibe to statin therapy compared with nondiabetic patients. Ezetimibe combination therapy with statin also demonstrates a lipid-altering efficacy with a greater between-treatment reduction in LDL-C, non-high-density lipoprotein cholesterol, and apolipoprotein B in patients with T2DM versus those without T2DM. In addition, a randomized, placebo-controlled study found that 2 months of ezetimibe combination therapy significantly decreased C-reactive protein (CRP) level, reduced visceral fat area and blood pressure, and increased plasma adiponectin level and insulin sensitivity compared to simvastatin alone in patients with hypercholesterolemia [12]. Pooled analysis of randomized, placebo-controlled trials focusing on individuals with hypercholesterolemia revealed that addition of ezetimibe to statin treatment led to a significant decrease in CRP level compared to using statins alone [13].

While statins are known to increase the risk of T2DM, studies have suggested that ezetimibe may have favorable effects on insulin resistance and hyperglycemia [14]. In high fat (HF)-diet-fed diabetic mouse models, ezetimibe supplementation significantly increased intestinal active glucagon-like peptide-1 level and significantly ameliorated insulin resistance induced by HF [15]. In patients with metabolic syndrome with coronary artery disease, ezetimibe reversed insulin resistance by reducing postprandial triglyceride and insulin levels [14]. Furthermore, the addition of ezetimibe to statin treatment showed a neutral effect on glucose metabolism, whereas high-intensity statin therapy was associated with a higher risk of incident diabetes in individuals with pre-diabetes [16]. A meta-analysis including 16 RCTs showed that the combination of ezetimibe with low-dose statin therapy did not significantly alter fasting glucose level or glycated hemoglobin compared to treatment with high-dose statins [17]. However, according to subgroup analysis, use of ezetimibe plus low-dose statin for more than three months showed a significant decrease in fasting glucose level compared to high-dose statin therapy [17].

The impact of ezetimibe in combination with statin therapy on coronary atherosclerosis has been explored. In the Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound Study (PRECISE-IVUS) trial, the combination of atorvastatin plus ezetimibe showed greater coronary plaque regression than atorvas-

tatin monotherapy in patients who underwent percutaneous coronary intervention [18]. The potential mechanisms underlying the greater reduction of atherosclerotic plaque progression attributed to ezetimibe have been explained by not only its cholesterol-lowering effects, but also its pleiotropic effects such as anti-inflammatory effects, reduction of the absorption of plant sterols, inhibition of smooth muscle cell proliferation, and anti-platelet effects [19]. Therefore, the addition of ezetimibe to statin therapy is anticipated to significantly improve the pathogenesis of atherosclerosis, especially in individuals with T2DM.

The residual cardiovascular risk associated with statin use can be attributed to molecular biological mechanisms that include an increase in atherogenic lipoproteins such as small dense LDL-C and remnant cholesterols, vascular injury and remodeling induced by inflammatory cytokines, and impaired reverse cholesterol transport [20]. Ezetimibe, which inhibits the absorption of cholesterol in the intestines, can reduce LDL-C level by an additional 20% when it is added to a statin therapy. Combination therapy with ezetimibe has the potential to lower the residual risk of cardiovascular disease associated with statin use through a variety of mechanisms beyond merely reducing lipid levels. Han et al. [10] found that, while statin/ezetimibe combination therapy more effectively reduced LDL-C level than statin monotherapy, it did not significantly improve insulin sensitivity or reduce vascular inflammation, particularly after adjusting for diabetes duration and hypertension. However, significant changes in HOMA-IR and PRDX4 were observed in the combination therapy group, with a greater than 50% reduction in LDL-C level prior to adjusting for covariates. Moreover, the duration of the study was relatively short. Therefore, extended long-term studies are required to confirm the influence of statin/ezetimibe combination therapy on insulin sensitivity and vascular inflammation in comparison with statin monotherapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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