Editorial

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Does Rosuvastatin/Ezetimibe Combination Therapy Offer Potential Benefits for Glucose Metabolism beyond Lipid-Lowering Efficacy in T2DM?

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Statins are widely prescribed lipid-lowering agents used for the prevention of cardiovascular diseases. However, several clinical trials and meta-analyses have reported that statin use is associated with an increased risk of new-onset diabetes and has adverse effects on glycemic homeostasis in a dose-dependent manner [1,2]. Notably, Asian populations are considered more susceptible to these adverse effects [3].

How statins increase the risk of new-onset type 2 diabetes mellitus (T2DM) is not fully understood [4], and several potential mechanisms have been proposed. One study suggests that statins may affect Ca^{2+} influx into pancreatic beta cells, thereby impairing insulin secretion. Another study proposes that statins might influence insulin receptor signaling, leading to changes in glucose transporter type 4 expression in adipose tissue, liver, and muscle, consequently increasing insulin resistance. Additionally, statins may affect microRNA expression, leading to epigenetic changes that impact glycemic homeostasis [4].

Although statins are necessary for most T2DM patients to modify cardiovascular risk, a combination therapy of statin and ezetimibe instead of high-dose statin alone can be considered as an option to address concerns regarding glycemic control. Statin/ezetimibe combination therapy has been shown to be non-inferior to statin monotherapy in terms of low-density lipoprotein cholesterol (LDL-C) lowering effects and achieving target LDL-C levels [5]. Moreover, it has demonstrated non-inferiority regarding one of the primary objectives of statin use, which is the improvement of major adverse cardiac events outcomes [6,7]. These findings suggest that such a combination therapy can effectively reduce LDL-C while potentially mitigating the risk of inadequate glucose control associated with high-dose statin therapy, offering a viable alternative for patients.

Recently, two similar studies comparing the effects of rosuvastatin/ezetimibe combination therapy and rosuvastatin monotherapy in patients with T2DM were published in the *Diabetes & Metabolism Journal*. In a study by Moon et al. [8], the efficacy of moderate-intensity rosuvastatin 10 mg/ezetimibe 10 mg combination therapy was compared to that of high-intensity rosuvastatin 20 mg monotherapy in high-risk patients with T2DM and 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥7.5%. After 24 weeks of treatment, the combination therapy group exhibited a greater reduction in LDL-C levels compared to the monotherapy group. Furthermore, homeostasis model assessment of β-cell function (HOMA-β) scores significantly improved in the combination therapy group without any changes in glycosylated hemoglobin levels. These findings suggest that such a combination therapy may provide additional benefits beyond the improvement of dyslipidemia [8].

Han et al. [9] conducted a study comparing the effects of rosuvastatin 5 mg monotherapy and a combination of rosuvastatin 5 mg and ezetimibe 10 mg on lipid profile, insulin sensitivity, and vascular inflammation in patients with T2DM and dyslipidemia. Over a 12-week period, the combination therapy

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group demonstrated significantly lower LDL-C levels compared to the monotherapy group. Additionally, among patients in the combination therapy group who achieved more than a 50% reduction in LDL-C, improvements were observed in homeostasis model assessment of insulin resistance (HOMA-IR) scores and levels of vascular inflammation marker peroxiredoxin 4. However, after adjusting for the duration of diabetes and hypertension, these changes did not reach statistical significance [9].

Both studies consistently demonstrated the superior LDL-C-lowering efficacy of rosuvastatin/ezetimibe combination therapy compared to rosuvastatin monotherapy, as well as extended benefits in terms of metabolic parameters [8,9]. Interestingly, there were observed differences in the effects on glycemic homeostasis parameters, specifically HOMA-IR and HOMA-β, between the two studies. Whereas HOMA-β as an insulin secretory function was significantly improved in the Moon et al. study [8] and HOMA-IR was not, the other study conducted by Han et al. [9] showed the opposite.

This discrepancy could be attributed to several factors, including variation in treatment regimens, treatment duration, and demographic features of the study populations. Firstly, Moon et al. [8] used different rosuvastatin doses (20 mg vs. 10 mg) for monotherapy and combination therapy, whereas Han et al. [9] used an identical dosage of rosuvastatin 5 mg in both treatment groups. Han et al. [9] showed that only nine individuals in the monotherapy group achieved a 50% reduction in LDL-C. The improvements in HOMA-IR and vascular inflammation markers shown by Han et al. [9] could be attributed more to the effect of LDL-C reduction rather than the effect of ezetimibe. Also, the longer treatment duration (24 weeks in Moon et al. [8] vs. 12 weeks in Han et al. [9]) might have allowed for more pronounced effects on HOMA-β to become evident compared to HOMA-IR. Additionally, there were differences in the baseline characteristics of the study populations. The subjects from Moon et al. [8] were relatively older, with a longer duration of DM, and had higher ASCVD risk. They also reported lower HOMA-β levels at baseline compared to those in Han et al. [9]. In contrast, baseline HOMA-IR was higher in Han et al. [9]. This indicates that patients with lower insulin secretion were more likely to be included in Moon et al. [8], while Han et al. [9] included patients with more insulin resistance. This heterogeneity of diabetes between the two studies might have affected response to ezetimibe.

Both studies were limited by a relatively small sample size. Nonetheless, they provide valuable insights into the comparative effects of rosuvastatin monotherapy versus rosuvastatin/ezetimibe combination therapy in patients with T2DM and dyslipidemia. These studies suggest that rosuvastatin/ezetimibe combination therapy may offer potential benefits for glucose homeostasis beyond LDL-C reduction in patients with T2DM. Further research is required to confirm the impact of ezetimibe on glucose homeostasis.

CONFLICTS OF INTEREST

Jun Sung Moon has been associate editor of the *Diabetes & Metabolism Journal* since 2022. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

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