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 Ca²⁺ 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...
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

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

REFERENCES

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