Statins Plus Metformin: A Promising Combination for Prevention and Treatment of Atherosclerosis

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Hypercholesterolemia, especially a high level of low density lipoprotein cholesterol (LDL-C), is one of the most important risk factors for atherosclerosis and that LDL-C is a pivotal therapeutic target. To date, statins have been found to be a safe and effective approach to reduce serum LDL-C levels, which is the cornerstone for primary and secondary prevention of atherosclerosis. However, regular statin monotherapy in some patients may not be sufficient to achieve a therapeutic LDL-C target. Every doubling of the statin dose reduces LDL-C levels by an additional 4–7%, whilst also increasing the incidence of adverse effects. It has been reported that statins increased the incidence of new-onset diabetes in a dose dependent manner especially in women, the elderly, or in the presence of a family history of type 2 diabetes (T2D) and Asian ethnicity.1 Recently, the IMPROVE-IT study, a randomized double blind clinical trial, has confirmed that combination lipid therapy (statins plus ezetimibe) could improve the efficacy without increasing side effects for atherosclerosis patients.2 This suggests that lipid lowering therapy with multiple medicines in combination may be a more effective alternative in future clinical practice.

Previous studies suggest that metformin, an old and effective antidiabetic medication, also possesses multiple cardioprotective effects, including anti-atherosclerosis.3-5 Recent research has shown that metformin significantly lowered blood levels of LDL-C by 11.83 mg/dL (P = 0.02) in patients with T2D.6 Glueck et al7 reported that in nondiabetic, morbidly obese subjects with body mass index greater than 30 kg/m2, metformin treatment for 29 weeks lowered LDL-C levels from 126 ± 34 mg/dL to 112 ± 43 mg/dL (P = 0.001), with a linear trend toward decreasing levels throughout (P = 0.036). It was believed that the effect of metformin was associated with adenosine 5-monophosphate-activated protein kinase (AMPK), AMPK activated by metformin can suppress fatty acid desaturases (FADS) synthesis in liver 6. It has been suggested that down-regulation of FADS could lower levels of arachidonic acid, leading to an increased membrane fluidity, and subsequently increases LDL receptor recycling, which accelerated the clearance of serum LDL-C.8 Thus, AMPK pathway may be the mechanism to clarify the benefits of additional lipid lowering effect of statins plus metformin strategy.

It has been reported that statins impair glucose metabolism via the following mechanisms. First of all, statins lower insulin secretion by inhibiting adenosine triphosphate (ATP)-dependent potassium channels and inducing inflammation, oxidation and apoptosis of β cells.1 Next, statins lower glucose transporter type 4 (GLUT4) expression, leading to impaired glucose uptake and insulin resistant in adipose tissue as well as muscle and liver.9-10 Metformin could reduce monocyte cytokine release and low-grade inflammation,11 which partly contributes to the improvement in insulin sensitivity. Moreover, metformin activated AMPK and subsequently increased GLUT4 expression and stimulated its translocation, resulting in ameliorating insulin sensitivity and increasing glucose uptake by other tissues.12,13

Highlights

Statin monotherapy in some patients will not be sufficient to achieve an LDL-C target and increase the incidence of new-onset diabetes in a dose dependent manner. Metformin, a safe and efficient medication for improving glucose metabolism, has been found to reduce LDL-C levels and has cardiac benefits for patients with T2D. Therefore, statins plus metformin may further reduce LDL-C levels and partly counteract statin-induced diabetes, which may be a promising therapeutic strategy.

Keywords: Statins, Metformin, Atherosclerosis, Lipid lowering therapy

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Thus, we speculate taking statins with metformin may partly counteract statin-induced diabetes.

Taken together, statins plus metformin may be a promising therapy strategy for patients with atherosclerosis especially those who coexist with impaired glucose tolerance via reducing serum LDL-C levels and improving the glucose metabolism impaired by statins. Although some slight adverse effects are reported in this combination therapy approach and renal function test is needed before and during the treatment, it is still a promising strategy overall."}

**Declaration of interests**

The authors declare no conflicts of interest.

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**References**


