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Editorial

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Postprandial Glucose and Triglyceride Increases Along with the Endothelial Malfunction were Attenuated by the Administration of SGLT2 Inhibitor, Empagliflozin

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In Japan, after the WWII, the prevalence of cardiovascular disease (CVD) increased in accordance with the increase in blood cholesterol levels due to the westernization of dietary habits. Along with the progress of the emergency system after the onset of CV events, the age-adjusted incidence rate due to CV events has decreased by the promotion of primary and secondary prevention of CV events using cholesterol-lowering drugs such as statins. The average blood cholesterol level has been decreased over the past decade due to the spread of proper diet and drug therapy, and on the other hand, the prevalence of glucose intolerance and diabetes mellitus (DM) has gradually increased along with the increase in visceral fat accumulation. Impaired glucose intolerance and DM are independent and strong risk factors for CV events; moreover, they exacerbate lipid metabolism (especially inducing hypertriglyceridemia and hypo-HDL cholesterolemia)[1]. Insulin resistance enhancement accumulates remnants, increases the proportion of small dense LDL, and enhances HDL clearance, thereby exacerbating atherogenicity[2]. Subanalysis of the Japan Diabetes Complications Study revealed that, in Japanese patients with DM, the increase in serum TG level was a leading predictor of coronary heart disease as well as serum LDL-C level[3]. Thus, in patients with impaired glucose tolerance or DM, the risk of CV events cannot be comprehensively reduced by conventional hypercholesterolemia treatment using statins only. Treatment for the clustering risk factors of CV events is needed for future control of cerebro- and cardiovascular risk.

In the recent progress for the therapeutic intervention for DM, selective inhibitors of sodium-glucose cotransporter 2 (SGLT2) inhibitor have shown the efficacy for decreasing "cardiovascular" events in recent major clinical trials[4, 5] and approved for the suitable drug in patients with both DM and cardiovascular events in some clinical guidelines[6, 7]. The results of the trials were that SGLT2 inhibitors were effective for reducing heart failure or CV death but did not accomplish to decrease CV events, such as angina pectoris, myocardial infarction, and/or acute coronary syndrome. In addition, the results of these trials have strong impact on the new era of reducing heart failure; however, there is no report that SGLT2-i potently and clearly reduced atherogenicity or regressed atherosclerotic plaques, resulting in reduced atherosclerotic CV diseases and their events. The dipeptidylpeptidase-4 inhibitor (DPP4-i), the most frequently used antidiabetic drugs in Japan, have been shown to be effective not only in impaired glucose tolerance but also in abnormal lipid metabolism, and in particular, remnant metabolism abnormality frequently associated with diabetes[8]. The accumulation of remnant lipoproteins is observed in patients with hypertriglyceridemia and hypo-HDL cholesterolemia, and the postprandial accumulation of remnants is linked to the impairment of endothelial function[9]. Postprandial increase in TG and remnants is related to the atherogenicity and the morbidity of CV disease, and the dual effect for improving atherogenic remnants and endothelial dysfunction is needed.

In this study, Sawada *et al.* examined the effect of the 6-month treatment of SGLT2-i empagliflozin on the postprandial lipid metabolism and endothelial dysfunction after the loading of fat and carbohydrates in subjects with ACS and type 2 DM[10]. In combination with the decrease in BMI and body fat percentage, not only HbA1c, fasting, and postprandial plasma glucose levels but also fasting and postprandial triglyc-

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eride levels were decreased significantly. And the strongest predictive factor of FMD improvement was found to be a change in plasma triglyceride levels. These results strongly and properly showed that SGLT2-I also improves glucose and lipid abnormalities in patients with both diabetes and dyslipidemia, resulting in the prevention of CV events in these patients.

Conflict of Interest

DM and SY receives clinical research funding from MSD, Bayer Yakuhin, Nippon Boehringer Ingelheim, Astrazeneca, Takeda Pharmaceutical Co., Astellas, Mitsubishi Tanabe, Kyowa Medex, Rohto, Fuji-Rebio company. SY receives honoraria from Kowa, Kowa-Souyaku, MSD, Bayer Yakuhin, Astellas-Amgen Biopharma, Sanofi, Skylight Biotech, East Japan Institute of technology. SY belongs to clinical course endowed by Izumisano city.

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