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REVIEW ARTICLE

Cardiovascular events and atherosclerosis in patients with type 2 diabetes and impaired glucose tolerance: What are the medical treatments to prevent cardiovascular events in such patients?

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ABSTRACT

Type 2 diabetes mellitus and impaired glucose tolerance (IGT) significantly induce advanced coronary artery disease and systemic atherosclerosis. Thus, type 2 diabetes mellitus and IGT are traditional risk factors of cardiovascular disease. In contrast, acute coronary syndrome is frequently caused by the rupture of coronary atherosclerotic plaques, which reduces patients' quality of life and might result in death. To date, many trials have sought to identify ways to determine the coronary plaque volume and its vulnerability, and many studies have shown that some specific antihyperglycemic agents might prevent coronary or carotid plaque progression, decrease plaque volume, induce plaque stability, and improve clinical outcomes in patients with type 2 diabetes mellitus and IGT. This article reviews the following: (i) the association between coronary or carotid plaques and abnormal glucose tolerance, including type 2 diabetes mellitus; and (ii) the effects of oral antihyperglycemic drugs to improve clinical outcomes and stabilize atherosclerotic plaques in patients with type 2 diabetes mellitus and IGT.

INTRODUCTION

Cardiovascular disease (CVD) is a significant cause of death, with >30% of all deaths worldwide likely caused by CVD[1]. Type 2 diabetes mellitus is a traditional risk factor for CVD, as well as dyslipidemia, hypertension, smoking and obesity. Patients with type 2 diabetes mellitus and impaired glucose tolerance (IGT) tend to have advanced coronary artery disease and systemic atherosclerosis.

A study carried out in Finland reported a significant higher incidence of myocardial infarction (MI) in patients with type 2 diabetes mellitus without previous MI than in those without diabetes or prior MI (18.8 vs 3.5%) during a 7-year follow-up period[2]. Furthermore, in patients with previous MI, the incidence of recurrent MI during the follow-up period was higher in patients with type 2 diabetes mellitus compared with that in patients without type 2 diabetes mellitus (45.0 vs 20.2%). Moreover, >40% of patients with both type 2 diabetes mellitus and previous MI died due to cardiovascular causes during the follow-up period. A subsequent 18-year follow-up study reported a similar trend[3].

There is a close relationship between abnormal glucose tolerance and type 2 diabetes and cardiovascular disease (Figure 1). Various mechanisms are possible to explain the relationship between abnormal glucose tolerance and poor clinical outcomes. Recent studies have suggested that type 2 diabetes mellitus and IGT are significant causes of coronary or plaque progression or systemic atherosclerosis, and affect plaque vulnerability[4–7]. This phenomenon is a possible explanation for the high incidence of CVD and mortality in patients with type 2 diabetes mellitus and IGT.

The present article examined the association between coronary or carotid plaques and abnormal glucose tolerance, including type 2 diabetes mellitus, and evaluated the effects of the oral antihyperglycemic drugs prescribed to improve clinical

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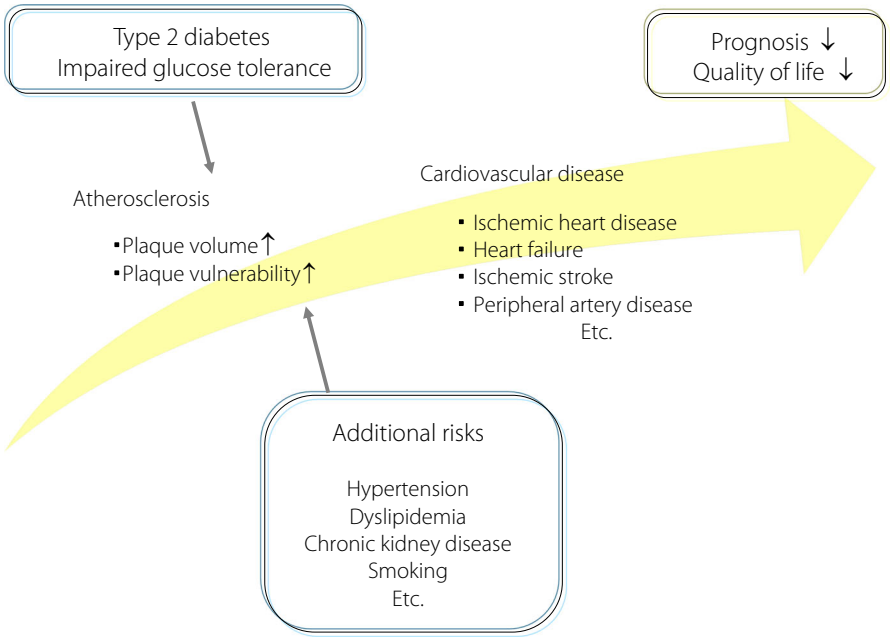

Figure 1 | Relationship between abnormal glucose tolerance and type 2 diabetes and cardiovascular disease.

outcomes and stabilize atherosclerotic plaques in patients with type 2 diabetes mellitus and IGT.

EVALUATION OF CORONARY ARTERY PLAQUES USING INTRAVASCULAR ULTRASOUND

Various imaging modalities with fine correlations with histological findings have been used to assess coronary plaques in clinical settings. In these settings, intravascular ultrasound (IVUS) provides precise information on coronary vessels and plaques[8–10]. Coronary plaque progression or regression remains a controversial surrogate for cardiovascular (CV) effects. However, one study showed that a positive linear relationship between the estimated risks of clinical events derived from three established risk scores (the German PROspective CArdiovascular Münster [PROCAM], Systematic COronary Risk Evaluation [SCORE] and Framingham), and the extent of coronary plaque progression, as measured by serial IVUS studies of coronary atherosclerotic plaques[11]. Furthermore, another study suggested a close relationship between the burden of coronary plaques, their progression and future CV events[12]. These findings suggest that coronary plaque progression and regression are important clinical markers.

The onset of acute coronary syndrome (ACS) is affected by coronary plaque progression or morphology[11,13]. The rupture of coronary atherosclerotic plaques and subsequent thrombosis are usually recognized as the primary mechanism of ACS, including acute MI and unstable angina pectoris[14–16]. In atherosclerosis, plaque vulnerability is strongly related to plaque rupture; furthermore, vulnerable plaques contain numerous inflammatory cells, particularly macrophages, suggesting that inflammation is closely associated with plaque instability[17–19]. Furthermore, vascular inflammation might begin in the very early phases of atherosclerotic lesions, and is deeply involved in the pathogenesis of atherosclerosis[20]. Lifestyle diseases significantly affect and lead to the progression of coronary plaque volume and composition, resulting in ACS induction. In addition, angiographically mild-to-moderate, but not necessarily severe, coronary artery stenosis sites must be considered in ACS cases. A study reported that major adverse CV events (death from cardiac causes, cardiac arrest, MI or re-hospitalization due to unstable or progressive angina) were nearly equally attributable to recurrence at the site of culprit and non-culprit lesions[21].

Once again, IVUS is a useful and popular technique[22–24]. Recently, integrated backscatter-IVUS, virtual histology (VH)-IVUS and near-infrared spectroscopy-IVUS have been applied to clearly show coronary plaque components[21,25,26]. Thus, both conventional IVUS and integrated backscatter-, VH- or near-infrared spectroscopy-IVUS help detect the volume, tissue components and vulnerability of coronary plaques with high-lipid core areas. In addition, findings from IVUS studies have shown a relationship between lifestyle diseases, such as metabolic syndrome and type 2 diabetes mellitus, coronary plaque volume and composition, and the therapeutic effects of some medicines related to coronary plaque reduction and stabilization[27–29].

In contrast, ultrasound evaluation of the carotid artery for atherosclerotic lesions is an established non-invasive and repeatable method[30,31] Furthermore, a significant correlation between coronary and carotid artery plaque instability has been observed[32]. Therefore, checking the carotid artery is also useful.

RELATIONSHIP BETWEEN TYPE 2 DIABETES MELLITUS OR IGT AND CORONARY PLAQUE

Reports have suggested that macrovascular disease gradually starts in the prediabetes stage[33]. Postprandial hyperglycemia, but not impairment of fasting glucose, increases the risk of CV events[34]. Survival rates after CVD in patients with diabetes and IGT are significantly lower than those after CVD in patients with normal glucose tolerance and impaired fasting glucose[34]. In addition, a close relationship has been reported between increased fasting plasma insulin concentration and the severity of coronary artery disease[35].

Using integrated backscatter-IVUS, Amano *et al.*[27] showed that the coronary lesions in patients with abnormal glucose regulation, including impaired glucose regulation and type 2 diabetes mellitus had more lipid-rich coronary plaques than those in patients with normal glucose regulation. In addition, the authors showed more lipid-rich coronary plaques in patients with metabolic syndrome compared with those without[28].

A VH-IVUS study showed that patients with diabetes frequently had increased dense calcium and necrotic core, and a higher frequency of thin-cap fibroatheroma and fibrocalcific atheroma, suggesting that atherosclerosis is more pronounced in the coronary artery in patients with type 2 diabetes mellitus than in those without[4].

Reports suggest that small dense low-density lipoprotein (LDL) particles are more atherogenic than large buoyant LDL particles, resulting in a high incidence of CVD[36,37]. IGT, postprandial hyperlipidemia and metabolic syndrome are associated with an increased number of small dense LDL particles[38–40]. The mean LDL particle size is significantly lower in patients with non-insulin-dependent diabetes with microalbuminuria compared with those in controls or patients without microalbuminuria; the LDL particle size is more decreased in those with macroalbuminuria[41]. Aggressive lipid-lowering therapy might contribute to a reduction in small dense LDL particles. Furthermore, a coronary IVUS study suggested that plaque regression induced by statin therapy is attenuated in patients with diabetes after ACS[42]. Therefore, a greater reduction in LDL cholesterol levels might be considered in patients with diabetes. Indeed, recent guidelines recommended aggressive therapies to lower LDL cholesterol levels in patients with type 2 diabetes mellitus under some specific conditions[36,43].

As shown above, for patients with type 2 diabetes mellitus and IGT, reducing CV events and atherosclerosis of the coronary and carotid arteries, as well as stabilizing vessel plaques are important treatment goals. Some non-insulin hypoglycemic agents have beneficial effects on these diseases (Table 1).

NON-INSULIN HYPOGLYCEMIC AGENTS AND CV EVENTS

Sulfonylurea

In the past, sulfonylurea (SU) drugs were the most widely used oral hypoglycemic agents. In contrast, in 1970, the University Group Diabetes Program showed that treatment with SU was associated with an increased risk of CV mortality[44]. It remains controversial whether SU itself progresses atherosclerosis and increases CV events[45,46]. SU has been used as the control agent when compared with various oral hypoglycemic agents from the viewpoint of anti-atherosclerotic effect.

One important issue is that SU drugs abolish myocardial protective mechanisms and might increase mortality in patients with type 2 diabetes mellitus[47,48]. Contrary to the mechanisms of SU, openers of adenosine triphosphate-sensitive K^+ channels, such as nicorandil, mimic cardiac ischemic preconditioning to limit MI size[49].

Metformin

Metformin is widely prescribed to lower blood glucose levels worldwide, as it might suppress excessive insulin secretion in patients with newly diagnosed type 2 diabetes mellitus. The UK Prospective Diabetes Study suggested that treatment with metformin has beneficial effects on CVD outcomes in overweight patients with type 2 diabetes mellitus, with a 36% relative risk reduction in all-cause mortality and a 39% relative risk reduction in MI compared with the conventional treatment[50]. However, a meta-analysis failed to show any beneficial effects of metformin in terms of reducing CV events[51].

There are limited data on the effects of metformin on the coronary artery. However, a meta-analysis of nine randomized clinical trials showed that treatment with metformin significantly reduced carotid intima-media thickness (IMT)[52]. As that study included patients with diabetes and abnormal glucose metabolism, metabolic syndrome, polycystic ovary syndrome, and coronary artery disease, but without diabetes, careful interpretation is required to evaluate the findings. However, metformin might have anti-atherogenic effects, resulting in a better prognosis in patients with specific conditions.

α-Glucosidase inhibitors

The use of α-glucosidase inhibitors delays the release of glucose from disaccharides and complex carbohydrates in the proximal small intestine, resulting in the modification of postprandial plasma glucose concentrations[53]. In 2002, the STOP-NIDDM trial research group showed that treatment with acarbose, an α-glucosidase inhibitor, significantly reduced the risk of diabetes, compared with placebo[54]. One year later, the group reported that acarbose also reduced the risk of CV disease in patients with IGT[55].

It remains unclear whether treatment with α-glucosidase inhibitors affects the coronary arteries. However, in patients with type 2 diabetes mellitus and IGT treated with acarbose, carotid IMT progressed slowly compared with that in controls[56,57]. In addition, IMT progression was significantly reduced in patients with type 2 diabetes mellitus treated with voglibose[58]. Therefore, α-glucosidase inhibitors are potential anti-atherosclerotic agents for the treatment of type 2 diabetes mellitus and IGT.

Table 1 | Non-insulin hypoglycemic agents and cardiovascular events

Oral hypoglycemic agents	Atherosclerotic CV events	Heart failure	Coronary plaque volume	Carotid intima-media thickness
Sulfonylurea drugs	?	?	?	?
Metformin	→~↓	?	?	↓
α-Glucosidase inhibitors	↓	?	?	↓
Pioglitazone	↓	↑	↓	↓
Dipeptidyl peptidase-4 inhibitors	→	→~↑(?)	?	↓
Sodium–glucose cotransporter 2 inhibitors	?	↓↓	?	?
Glucagon-like peptide-1 receptor agonists	↓	→~↑	?	?

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-Γ AGONIST (PIOGLITAZONE)

Pioglitazone is an insulin sensitizer that directly binds and activates peroxisome proliferator-activated receptor-γ, thereby reducing insulin resistance[59]. In the PROactive study, compared with matching placebo, the composite of all-cause mortality, non-fatal MI and stroke as the main secondary end-point was significantly reduced in patients with type 2 diabetes mellitus treated with pioglitazone with evidence of macrovascular disease[60]. The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial showed that pioglitazone slowed the progression of carotid IMT in patients with type 2 diabetes mellitus, compared with glimepiride[61].

In addition, compared with glimepiride, treatment with pioglitazone resulted in a significant reduction in coronary plaque volume in patients with type 2 diabetes mellitus[62]. In addition, a VH-IVUS trial reported that treatment with pioglitazone reduced the necrotic core component in patients with type 2 diabetes mellitus with stable angina, suggesting that coronary plaques might be stabilized[63]. The potential anti-atherogenic effects of pioglitazone include improved insulin sensitivity, increased plasma adiponectin levels and anti-oxidant activity[64,65].

However, treatment with pioglitazone increases water retention; therefore, it should be avoided in patients with heart failure[66]. In addition, pioglitazone might increase the risk of bladder cancer, although the evidence is contradictory[67,68].

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Unfortunately, treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors did not significantly improve CV events in patients with type 2 diabetes mellitus and CVD or those at risk for CV events compared with placebo or control[69,70].

Evidence is limited regarding the effects of DPP-4 inhibitors on the coronary artery in patients with type 2 diabetes mellitus and IGT. In contrast, treatment with sitagliptin effectively prevented carotid IMT progression in patients with both coronary artery disease and mild type 2 diabetes mellitus or IGT[71]. A similar effect of sitagliptin was reported in patients with type 2 diabetes mellitus treated with insulin without a history of apparent CVD[72]. However, data on DPP-4 inhibitor treatment leading to coronary plaque regression are limited.

Because DPP-4 inhibitors might exert anti-atherosclerotic effects, a clinical trial with an extended observation period might help to assess their efficacy in preventing CV events.

SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

The use of sodium–glucose cotransporter 2 (SGLT2) inhibitors, novel glucose-lowering drugs, such as empagliflozin and canagliflozin, resulted in remarkable improvement in CVD outcomes among patients with type 2 diabetes mellitus, and established CVD or high CV risks in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial and Canagliflozin Cardiovascular Assessment Study (CANVAS) Program[73,74]. In particular, the beneficial effects of SGLT2 inhibitors in preventing readmission due to heart failure and reducing CV mortality in patients with heart failure were shown in patients with and without diabetes[75,76].

A recent meta-analysis of data from various clinical development programs with different risk categories showed that treatment with dapagliflozin reduced the incidence of MI compared with control[77]. However, a recent post-hoc analysis of the CANVAS and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials failed to show a reduction in the overall incidence of MI in patients with type 2 diabetes mellitus with a history or high risk of CV disease or in those with chronic kidney disease[78]. Interestingly, in the study, treatment with canagliflozin in the CANVAS Program was associated with a lower risk of non-ST elevation MI, but a higher risk of ST elevation MI[78]. Further investigations are warranted to confirm the effects of SGLT-2 inhibitors on the prevention of atherosclerotic diseases.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Glucagon-like peptide (GLP)-1 receptor agonists have beneficial effects in preventing CV events in patients with diabetes and established CVD, with a reduction in atherosclerosis-related events in patients treated with GLP-1 analogs[79,80]. However, data are limited regarding the precise mechanisms of

anti-atherosclerosis, and solid IVUS and IMT evaluations are lacking. In addition, there is a concern regarding increased heart rates in patients with systolic heart failure with or without type 2 diabetes mellitus treated with liraglutide[81]. Thus, SGLT-2 inhibitors and GLP-1 analogs might differ in their ability to prevent CV events.

An *in vitro* study suggested that GLP-1 mediates cardioprotection by mimicking remote ischemic conditioning[82]. It is possible that through this mechanism, the cardioprotective effects are induced by a GLP-1 receptor agonist.

CONCLUSION

Various medications have proven to be effective in preventing adverse CV events. Recent guidelines for the treatment of diabetes or prediabetes should be followed[83–85]. Multifactorial interventions for modifiable risk factors reduce CVD in patients with diabetes[86].

During the coronavirus disease 2019 (COVID-19) pandemic, poor glycemic control might result in increased CVD risk. Furthermore, overwhelmed medical systems during the pandemic are becoming a social problem, despite doctor and medical staff efforts[87–89]. Therefore, we have to pay attention to such severe situations and should improve the clinical status of patients with high risks, such as diabetes.

DISCLOSURE

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