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The Difference between SGLT2 and DPP-4 Inhibitors on Glucose Fluctuation in Patients with Type 2 Diabetes

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Abstract

Various oral and parental hypoglycemic agents have been developed to achieve adequate glycemic control in patients with type 2 diabetes mellitus. Because of the relatively high prevalence of cardiovascular events in this patient population, it is also necessary to minimize glucose fluctuation to prevent atherosclerotic disease. Two different types of hypoglycemic agents, dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors, appear to control glucose variability to a similar extent, but their efficacy might depend somewhat on the patient's background. To clarify which type of drug is more appropriate for use in a given patient, further investigation is needed.

Keywords: Glucose fluctuation; Dipeptidyl peptidase-4 inhibitors; Sodium-glucose co-transporter 2 inhibitors; Type 2 diabetes mellitus

Abbreviations

CKD: Chronic Kidney Disease; DPP-4: Dipeptidyl Peptidase-4; GIP: Glucose-dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; SGLT2: Sodium-Glucose Co-Transporter 2; T2DM: Type 2 Diabetes Mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is generally characterized by insulin resistance and insufficient insulin secretion on demand. The management of multiple metabolic aspects of the condition is critical to avoid the development of several types of complications, including cardiovascular disease. It has been established that patients with T2DM have a 2- to 4-fold higher risk of atherosclerotic disease than those without the condition [1-3], resulting in lower mortality [4]. Although the comprehensive treatment of various metabolic abnormalities

has succeeded in consistently reducing both micro and macrovascular events [5], death rates remains higher in patients with T2DM [6]. Additional strategies may be necessary alongside current diabetic care, for example improved control of HbA1c levels, blood pressure, and lipids. In this context, more intensive or earlier treatment of atherosclerotic risk factors might represent a suitable approach. In this review, we discuss the importance of managing glucose fluctuations, which can lead to the development of atherosclerotic disease, and evaluate the effects of two frequently used types of anti-diabetic agent, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors, on glucose variability based on our clinical study and previous evidence.

Glucose Fluctuation and Atherosclerotic Disease

As described above, patients with T2DM are at significant risk of developing atherosclerotic disease. In addition, clinical studies have demonstrated that cardiovascular risk increases even with impaired glucose tolerance, which is characterized by temporarily elevated post-prandial serum glucose levels resulting from insufficient insulin secretion [7].

The concept of glucose fluctuation has become increasingly important, and many studies have verified that glucose fluctuation itself is closely related to the surrogate markers of atherosclerosis [8-10] and endothelial cell damage, thought to represent a first step in atherosclerotic changes in blood vessels [11]. *In vitro* studies in which endothelial cell were exposed to high and low glucose concentrations alternately showed increased cell apoptosis accompanied by high Bax gene expression compared with continuous high-glucose conditions [12]. From a clinical perspective, it remains unclear whether such glucose fluctuations are directly related to decrease mortality because evidence supporting such a relationship is insufficient. However, accumulating evidence that patients with impaired endothelial cell function are more likely to experience cardiovascular events [13] in addition to the *in vitro* experiments described above indicates the importance of this hypothesis.

Taken together, the achievement of satisfactory levels of glycemic surrogate markers, such as HbA1c and glycoalbumin, as well as reducing glucose fluctuations is important for preventing the development of atherosclerotic disease. Hypoglycemic agents who achieve these treatment goals are therefore clearly beneficial.

Anti-Diabetic Therapies and Glucose Fluctuation

To date, numerous types of oral or parental hypoglycemic agents are available to achieve improved glycemic control in patients T2DM, although therapies which can suppress glucose fluctuations are limited. Among these, DPP-4 inhibitors, which are incretin-related drugs, and SGLT2 inhibitors are widely used because of their safety and ability to exert several pleomorphic effects. Incretin-related drugs show not only anti-hypoglycemic but also anti-atherosclerotic activity based on numerous *ex vivo* and *in vivo* studies [14-16]. Incretin monotherapy is rarely associated with hypoglycemia because of its glucose level-dependent hypoglycemic actions; briefly, under conditions of hyperglycemia, increased levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) potently enhance insulin action. However, under normal or hypoglycemic conditions, GLP-1 secretion is inhibited, insulin secretion action does not occur, and the glucagon response is improved via the action of GIP [17] with the result that glucose variability appears to be effectively suppressed. Despite this ideal mechanism, however, prospective clinical trials to targeting the suppression of cardiovascular events failed to prove the superiority of these agents [18-20]. In addition, controversial results on the effects of incretin on surrogate markers of cardiovascular risks, such as flow mediated dilatation and intra-media thickness, have been reported [21-23].

The hypoglycemic action of SGLT2 inhibitors also relies, in part, on serum glucose concentration. In general, the efficacy of SGLT2 inhibitors is closely related to the filtered load of glucose, and thus they exert potent hypoglycemic activity under hyperglycemic conditions [24]. If tubular glucose uptake decreases under hypoglycemic conditions, glucose reabsorption is partially compensated by SGLT1 overexpression when SGLT2 is inhibited [25]. Moreover, hepatic gluconeogenesis, lipolysis, and increased glucagon prevent hypoglycemia and can inhibit glucose variability [26,27]. The glucose-lowering effect of SGLT2 inhibitors is thought to function in an insulin-independent manner, and hypoglycemic and glucose-level flattening effects have been confirmed in patients with type 1 diabetes [28]. Recent clinical trials have demonstrated surprising anti-cardiovascular effects associated with some types of SGLT2 inhibitors [29,30], but it remains unclear how and which aspect of their metabolic effects leads to such dramatic effects.

In such situations, it is worth assessing which of these agents can more effectively inhibit glucose fluctuation. Recently, we conducted a randomized prospective trial to assess the effect of switching from a DPP-4 inhibitor to an SGLT2 inhibitor on glucose fluctuation in patients with T2DM on insulin. In summary, continuous glucose monitoring showed little

difference in all-day, day-time, and night-time glucose fluctuation between the types of inhibitors (**Table 1**) [31].

Table 1 Summary of the effects on glucose fluctuation of switching from DPP-4 inhibitors to the SGLT2 inhibitor, dapagliflozin, in patients with type 2 diabetes mellitus receiving insulin.

	DPP-4 inhibitors to Dapagliflozin
HbA1c	→
Glucose fluctuation	
All-day	→
Night-time	→
Prevalence of hyperglycemia	→
Prevalence of hypoglycemia	→
Body weight	Improve
Lipid metabolism	→
Liver function	Improve
Renal function	→
Albuminuria	Tendency to improve
DPP-4: dipeptidyl peptidase-4; SGLT2: Sodium-glucose co-transporter 2	

Similarly, Okajima et al. reported on another randomized controlled trial comparing monotherapy of a DPP-4 inhibitor or SGLT2 inhibitor and a combination of these inhibitors on multiple daily injection of insulin. No significant differences were observed in all-day glucose fluctuation among the treatment arms, but protocols containing SGLT2 inhibitors showed a significantly reduced incidence of night-time hypoglycemia compared with insulin monotherapy [32]. Although studies comparing the effects of DPP-4 inhibitors and SGLT2 inhibitors on glucose fluctuation are limited, these results suggest that these agents appear to control glucose variability with equal efficacy.

Effects of DPP-4 Inhibitors and SGLT2 Inhibitors on Glucose Fluctuation in Patients with Chronic Kidney Disease

Several types of metabolic disorders, including T2DM, are associated with increased risk of chronic kidney disease (CKD). Indeed, 30%–40% of patients with T2DM suffer from micro- and macro-albuminuria [33,34]. Importantly, optimum glycemic control has been shown to prevent the progression of CKD and can achieve remission of diabetic nephropathy [35]. However, as many pharmacological agents are excreted and metabolized via the kidney, the use of anti-diabetic agents is limited in patients with impaired renal function. In addition, CKD is also associated with increased risk of cardio-cerebral disease [36], hence the prevention of atherosclerotic disease is important in patients with CKD. In this context, anti-diabetic agents who exert preferable effects in both CKD and cardiovascular diseases are desirable.

Both DPP-4 inhibitors and SGLT2 inhibitors have been proposed to exert some pleomorphic effects, including renal protection (**Table 2**). Previous *in vitro* and *in vivo* studies have verified that incretin agents, including DPP-4 inhibitors, exert renal protective effects against increased renal oxidative stress under hyperglycemic conditions via cAMP-PKA activation [37]; stromal cell-derived factor 1 upregulation and stromal cell-derived factor 1-dependent anti-oxidative and anti-fibrotic effects on the diabetic kidney [38]; and inhibition of endothelial-to-mesenchymal transition and renal fibrosis via suppression of endothelium DPP-4 and integrin β 1 levels [39]. In clinical use, some pooled analysis and randomized controlled trials using DPP-4 inhibitors resulted in significant improvement of albuminuria [40,41]. Moreover, the EMPA-REG trial showed that treatment with empagliflozin, an SGLT2 inhibitor, was associated with slower progression of CKD and lower rates of clinically relevant renal events [42]. These renal protective effects have recently been attributed to the normalization of tubuloglomerular feedback and glomerular hyper-filtration [43], hematopoietic action via erythropoietin elevation [42], and improved renal efficacy and function as a result of increased levels of ketone bodies [44].

Table 2 Comparison of the effects of DPP-4 and SGLT2 inhibitors on metabolic parameters.

	DPP-4 inhibitors	SGLT2 inhibitors
Glycemic control (HbA1c etc.)	Improve	Improve (weakened under renal dysfunction)
Glucose fluctuation	Improve	Improve (weakened under renal dysfunction)
Body weight	Not change	Improve
Lipid metabolism	Improve	Improve
Preferable effects on		
Cardiovascular	+	++
Kidney	+	+
Liver	+	++
DPP-4: Dipeptidyl peptidase-4; SGLT2: Sodium-glucose co-transporter 2		

So, how do the effects of these classes of inhibitors on glucose fluctuation differ in CKD? Although some types of DPP-4 inhibitors require dose reduction according to their prescribing information, previous meta-analyses have shown that incretin therapies, including DPP-4 inhibitors, effectively controlled HbA1c levels in moderate or severe renal dysfunction [33,45]. Even under hemodialytic conditions, glucose fluctuation could be ameliorated using teneligliptin [46]. In contrast, the efficacy of SGLT2 inhibitors on hypoglycemic action and glucose fluctuation appears somewhat diminished in renal dysfunction [47]. Ferrannini et al. showed that glucose excretion with ipragliflozin treatment relied on both renal function and serum glucose levels [24]. Our previous study on the switching of DPP-4 inhibitors to the SGLT2 inhibitor dapagliflozin also showed that patients with relatively impaired renal function did show an

improvement in glucose fluctuation [31]. Taken together, SGLT2 inhibitors appear to require relatively normal renal function in order for glucose fluctuation to be effectively managed.

Summary

Both DPP-4 and SGLT2 inhibitors can effectively suppress glucose fluctuation in hyperglycemia, but the underlying mechanisms are different. Patients with T2DM tend to have metabolic disorders other than problems with glycemic control and these must be taken into consideration when selecting the appropriate treatment regimen. Although we have examined the relationship between renal dysfunction and glucose fluctuation, it remains uncertain which patients might benefit the most from these drugs. Further investigation is therefore required to clarify this.

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Conflicts of Interest

HM has received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Daiinippon Pharma Co., Eli Lilly, Kissei, Mitsubishi Tanabe Pharma Co., MSD, Novo Nordisk Pharma, and Sanofi, and has received research funding from Astellas Pharma Inc., AstraZeneca, Eli Lilly, and Mitsubishi Tanabe Pharma Co.

HN has no conflicts of interest to declare.

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