Glycemic Control in Elderly Patients with Type 2 Diabetes Mellitus: The Importance of Preventing Hypoglycemia Especially in Patients with Chronic Kidney Disease

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The prevalence of patients with type 2 diabetes mellitus (T2DM) continues to increase. One primary concern in the patients with T2DM is the development of various complications, including retinopathy, nephropathy, neuropathy, myocardial infarction, and stroke; their prevention is the main treatment goal in T2DM. Furthermore, the frequencies of dementia, sarcopenia, and cancer are also higher in elderly patients with T2DM. Numerous clinical trials reveal that improving glycemic control can mitigate complications. In addition, hypoglycemia is associated with increased rates of dementia and cardiovascular death.

Over the last several decades, the treatment strategies for T2DM have changed with the improved understanding of the underlying pathophysiology and the development of many glucose-lowering drugs. Sulfonylureas and glinides promote the secretion of insulin, α-glucosidase inhibitors suppress the absorption of glucose from the intestinal tract, biguanides suppress the hepatic production of glucose, and thiazolidinediones improve the action of insulin in the liver and muscles. Additionally, dipeptidyl peptidase-4 inhibitors and glucagon like peptide–1 receptor agonists promote the secretion of insulin in a glucose–dependent manner, whereas sodium glucose cotransporter 2 inhibitors reduce glucose reabsorption in the proximal renal tubules and urinary glucose excretion. Sulfonylureas are prone to precipitate hypoglycemia in patients with renal dysfunction. It is important for patients to understand the symptoms of hypoglycemia for appropriate resolution.

Appropriate selection of glucose-lowering drugs based on the condition of the individual patient is necessary for better control of the onset and the progression of complications and to achieve better glycemic control without causing hypoglycemia.

Key words: hypoglycemia, kidney dysfunction, type 2 diabetes mellitus (T2DM)
to postprandial hyperglycemia. T2DM is an independent risk factor for retinopathy, nephropathy, and neuropathy as well as cardiovascular morbidity and mortality. Furthermore, T2DM is an important risk factor for dementia. Recent evidence suggests that T2DM is also a risk factor for cognitive dysfunction and physical disability. Subsequently, these complications have a deleterious effect on the quality of life in patients with T2DM. Prospective studies have shown an association between the degree of hyperglycemia and the increased risk of microvascular complications, sensory neuropathy, myocardial infarction, stroke, macrovascular mortality, and all-cause mortality.

The influence of hypoglycemia on the complications of T2DM

Severe hypoglycemia is associated with an increased risk for cardiovascular disease. Hypoglycemia induces several counter-regulatory responses including decreased insulin secretion from pancreatic β cell, increased glucagon secretion from pancreatic α cells, increased sympathoadrenal response with acute increases in plasma adrenaline and norepinephrine levels, increased secretion of adrenocorticotrophic hormone/glucocorticoids. Specifically, hypoglycemia induces the release of catecholamines, which have profound effects on the myocardium and blood vessels by increasing myocardial contractility, myocardial workload, and cardiac output. These effects can induce ischemia in the myocardium of patients with coronary artery disease. In addition to these responses, hypoglycemia also induces several indirect changes that impact the inflammatory cytokine secretion, endothelial function, coagulation, and fibrinolysis. All these responses have potential adverse effects on cardiovascular morbidity and mortality. In support of these potential adverse outcomes of hypoglycemia, ORIGIN (Outcomes Reduction with Initial Glargine Intervention) trial showed that both severe hypoglycemia and nocturnal severe hypoglycemia independently predicted cardiovascular events and mortality in patients with T2DM.

Furthermore, severe hypoglycemia is associated with reduced cognitive function, and patients with poor cognitive function have more severe hypoglycemia. While most hypoglycemia is mild and self-managed, more severe hypoglycemia may require hospitalization; result in hypoglycemic coma, brain damage, or both; and affect the blood-brain barrier integrity. These effects of severe hypoglycemia are associated with an increased risk of subsequent dementia. Severe hypoglycemia is known to induce focal neurological deficits and transient ischemic attacks, which are reversible with the correction of blood glucose levels. Recent evidence also suggests that recurrent or severe hypoglycemia may predispose patients to long-term cognitive dysfunction and dementia based on the evidence showing that patients with multiple episodes of hypoglycemia had a graded increase in dementia risk. Conversely, severe cognitive dysfunction is associated with an increased risk of hypoglycemia. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, severe cognitive dysfunction was associated with a two-fold increase in the risk of severe hypoglycemia. The Fremantle Diabetes Study found that dementia was a risk factor for hypoglycemia as well.

The characteristics of hypoglycemic symptoms in elderly patients with T2DM

Hypoglycemia is defined as a plasma glucose level below 70 mg/dl, at which time the brain becomes neuroglucopenic and promotes the secretion of counter-regulatory hormones, primarily the adrenergic hormone adrenaline and the neurotransmitter norepinephrine, which have relevant cardiovascular effects. This effect occurs in the absence of the warning symptoms of hypoglycemia, which normally occur in patients with lower plasma glucose levels below 60 mg/dl. Studies have reported that the distinct awareness of hypoglycemia in the presence of pronounced hypoglycemia led to prolonged reaction times in elderly patients with T2DM. In contrast to middle-aged patients with T2DM, those over the age of 65 years fail to perceive neuroglycopenic and autonomic hypoglycemic symptoms even in the presence of a comparably prolonged reaction time induced by hypoglycemia. The age-related impairment of hypoglycemia awareness was shown to be independent of alterations in the neuroendocrine counter-regulation.
because hormonal responses to hypoglycemia were similar between the two age-groups. These findings may, at least in part, explain why elderly patients are at a particularly high risk of severe hypoglycemic episodes. Thus, hypoglycemia unawareness increases the risk of prolonged, more frequent hypoglycemia. These events perpetrate a deleterious vicious circle, leading to an increase in severe hypoglycemia with brain dysfunction.

The characteristics of elderly patients with T2DM

Hyperglycemia is a risk factor for both diabetic microangiopathy and macroangiopathy in elderly patients with T2DM. In addition, elderly patients with T2DM are susceptible to postprandial hyperglycemia and particularly hypoglycemia. Furthermore, older age tends to be associated with renal dysfunction, and elderly patients are more susceptible to drug interactions and suffer more frequently from age-related syndromes such as dementia, cognitive impairment, depression, and sarcopenia. Therefore, several additional aspects should be considered during the implementation of glycemic control in elderly patients with T2DM. The glucose-lowering drugs used elderly patients with T2DM should be selected with consideration given to their physical and cognitive function, socioeconomic status, adherence, and personal preferences. Furthermore, elderly patients on glucose-lowering drugs should be monitored for related adverse events such as hypoglycemia and should be instructed on nonspecific hypoglycemic symptoms and the treatment of hypoglycemia. Particularly, careful attention should be paid to severe hypoglycemia in elderly diabetic patients with renal dysfunction.

The management of glycemic control in elderly patients with T2DM

In Japan, the new glycemic control target was announced in 2013. A hemoglobin A1c (HbA1c) level of less than 7.0% is recommended as the target for the prevention of complications, whereas HbA1c of less than 6.0% and treatment intensification are recommended as targets for normalizing blood glucose levels. An HbA1c level of less than 8.0% is recommended goal in challenging cases, and the treatment targets are recommended to be set with consideration of age, disease duration, organ dysfunction, risk of hypoglycemia, and the patient’s support system. Furthermore, the goals for glycemic control in elderly diabetic patients were also announced in 2016 (Figure-1). In short, for elderly patients, the glycemic target should be determined for each patient by taking the basic and instrumental activities of daily living, cognitive function, age, duration of diabetes, risk of hypoglycemia, any support available to the patient, and dysfunction of comorbidities into consideration, while noting the potential risk of hypoglycemia that increases with age in those patients. First, the glycemic target in the elderly is classified into categories I to III based on the evaluation of cognitive function as well as basic and instrumental activities of daily living. Second, the glycemic target in the elderly is classified according to the drugs that are potentially associated with severe hypoglycemia, such as insulin, sulfonylureas, and glinides. In patients not using any of these drugs, the glycemic target in categories I and II is set to an HbA1c level of less than 7.0%; the glycemic target in category III is set to an HbA1c level of less than 8.0%. For patients treated with these drugs, category I comprises those aged more than 65 years but less than 75 years and those aged more than 75 years. The glycemic target in category I patients aged more than 65 years but less than 75 years is set to an HbA1c level of less than 7.5%, the glycemic target in patients aged more than 75 years in category I and those in category II is set to an HbA1c level of less than 8.0%, and the glycemic target in category III patients is set to an HbA1c level of less than 8.5%. Importantly, in patient on drugs with potential severe hypoglycemia, the glycemic target is lower for all categories. Specifically, the lower limits of HbA1c for category I (aged more than 65 years but less than 75 years), I (aged more than 75 years), II, and III are 7.5%, 8.0%, 8.0%, and 8.5%, respectively. These glycemic targets are designed to prevent severe hypoglycemia in elderly patients. The elderly have specific health issues that may vary widely among individuals. In particular, susceptibility to severe hypoglycemia is a hallmark of elderly diabetes. Severe hypoglycemia not only impairs cognitive function but also can increase the risk of cardiovascular events.
The characteristics of glucose-lowering drugs

Over the last several decades, the treatment strategies for T2DM have changed with the improved understanding of the underlying pathophysiology and the development of many glucose-lowering drugs. As shown in Figure-2, the glucose-lowering drugs can be mainly classified into “insulin” and “non-insulin secretagogues”. Insulin secretagogues include sulfonylureas, fast-acting insulin secretagogues (glinides), dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon like peptide-1 (GLP-1) receptor agonists. DPP-4 inhibitors and GLP-1 receptor agonists are less likely to induce hypoglycemia because they are glucose-dependent insulin secretagogues. In addition, non-insulin secretagogues including thiazolidinediones, biguanides, α-glucosidase inhibitors, and sodium glucose cotransporter 2 (SGLT2) inhibitors, are also less likely to induce hypoglycemia.

The characteristics of each glucose-lowering drug are summarized below.

1. Insulin secretagogues

1) Glucose-independent insulin secretagogues

➤Sulfonylureas: Sulfonylureas bind to the sulfonylurea receptors on the pancreatic β cells to stimulate insulin secretion to potently lower blood glucose levels. However, after good glycemic control has been achieved, patients should be ensured not to develop hypoglycemia before meals and not to delay meals. Therefore, constant attention is required especially in elderly patients. In cases of doubt, the sulfonylurea dosage should be reduced. In certain cases, hypoglycemia can occur even with low drug doses. Additionally, there is a risk of prolonged hypoglycemia in elderly patients with renal dysfunction; therefore, careful attention is warranted in these patients as well.

➤Glinides: Glinides improve postprandial hyperglycemia by immediately promoting insulin
secretion. As short-acting insulin secretagogues, glinides are less frequently associated with the risk of hypoglycemia.

2) Glucose-dependent insulin secretagogues

➢ **DPP-4 inhibitors**: DPP-4 inhibitors are gastrointestinal peptides that enhance the secretion of insulin from pancreatic β cells and suppress the glucagon release from pancreatic α cells in a glucose-dependent manner. Thus, DPP-4 inhibitors improve both fasting and postprandial hyperglycemia. DPP-4 inhibitors are associated with a low risk of hypoglycemia, are weight neutral, and have been shown to improve pancreatic β cell function in *in vitro* and *in vivo* animal studies. While the risk of hypoglycemia with DPP-4 inhibitor monotherapy is low, therapy including DPP-4 inhibitors in combination with sulfonylureas or insulin often increases the risk of hypoglycemia, underlying the rationale for reducing the dose of either drug in patients on combination therapy. DPP-4 inhibitors were previously considered to be associated with increased risk of acute pancreatitis, pancreatic cancer, and infections; however, current evidence argues against these associations.

➢ **GLP-1 receptor agonists**: GLP-1 receptor agonists, which are available as injectable drugs,
promote postprandial insulin secretion in a glucose-dependent manner while concomitantly inhibiting glucagon secretion. Thus, GLP-1 receptor agonists improve both fasting while postprandial hyperglycemia and are associated with the risk of hypoglycemia to a lesser extent. While these drugs have also been shown to exert their glucose-lowering effect when administered in combination with sulfonylureas or insulin, such combination therapies have been shown to be associated with an increased risk of hypoglycemia, suggesting the rationale for reducing the dose of either drug. GLP-1 receptor agonists are associated with gastrointestinal symptoms; to alleviate their onset, GLP-1 receptor agonists need to be initiated at a low dose and titrated up as required. GLP-1 agonists were previously considered to be associated with increased risk of acute pancreatitis and pancreatic cancer; however, current evidence argues against these potentially fatal complications.

2. Non–insulin secretagogues

➢ Thiazolidinediones: Thiazolidinediones improve glycemic control by promoting peripheral insulin sensitivity and inhibiting hepatic glucose release. Thiazolidinediones are often associated with weight gain due to their ability to promote fluid retention and adipocyte differentiation, and patients on thiazolidinediones require monitoring for edema. Fractures are also associated with the use of thiazolidinediones.

➢ Biguanides: Biguanides, which are currently used as first-line glucose-lowering drugs in Western countries, exert their effect by inhibiting hepatic glucose production and improving peripheral insulin sensitivity. Rarely, biguanides are associated with lactic acidosis. Constant attention is necessary especially in patients with renal dysfunction. Furthermore, additional attention is necessary in elderly patients with renal dysfunction due to the higher risk of lactic acidosis.

➢ α-glucosidase inhibitors: α-Glucosidase inhibitors that inhibit intestinal glycolysis and delay intestinal glucose absorption suppress postprandial hyperglycemia and hyperinsulinemia and should be taken immediately before meals. However, α-glucosidase inhibitors are also often associated with flatus and diarrhea. Hypoglycemia in patients treated with α-glucosidase inhibitors requires only glucose intake to improve hypoglycemia.

➢ SGLT2 inhibitors: SGLT2 inhibitors are a new class of non–insulin secretagogues approved to lower glucose lowering in patients with T2DM in Japan since 2014. SGLT2 inhibitors increase urinary glucose excretion by reducing the reabsorption of the filtered glucose in the renal proximal tubules, thereby improving hyperglycemia in patients with T2DM. SGLT2 inhibition occurs independently of insulin secretion and is not affected by pancreatic β cell function or the degree of insulin resistance. SGLT2 inhibitors also provide mild osmotic diuresis and net caloric loss, contributing to a reduction in body weight and blood pressure. Current evidence demonstrates that SGLT2 inhibitors reduce cardiovascular events, hospitalization for heart failure, and kidney failure. Conversely, SGLT2 inhibitors are associated with an increased frequency of urinary tract and genital infections as adverse effects. Other adverse effects include dehydration accompanied by symptoms such as thirst, polyuria, and hypotension; dehydration associated thromboembolism and related cerebral infarction; events associated with increased ketone bodies; and rash.

Treatment with glucose-lowering drugs

The choice of glucose-lowering drugs should be tailored for each patient according to the disease condition, with additional attention paid to their pharmacological and safety profiles. With informed consent obtained from the patient, the drugs should be initiated at a low dose and gradually titrated up depending on the glycemic control required at that time. In patients failing to achieve their glycemic target while on monotherapy with a first-line drug, consideration may be given to increasing the dose of the first-line drug, switching to a more potent glucose-lowering drug, or combining the first-line drug with another glucose-lowering drug with a different mechanism of action. No clear synergistic effects have been demonstrated among the drugs used in combinations, and no guidelines have been established for combination therapies using glucose-lowering drugs. However, in patients with inadequate glycemic control despite monotherapy with sulfonylureas or metformin, combination therapy with
another glucose-lowering drug utilizing a different mechanism of action is usually considered; combination therapy with these drugs has shown to be effective for lowering glucose levels. Combination therapy with three or more drugs has been shown to be effective for lowering glucose levels as well.

**The indications for insulin therapy**

Insulin therapy is implemented in patients with T2DM who suffer from inadequate glycemic control despite medical nutrition therapy, increased physical activity, and therapy with non–insulin glucose-lowering drugs. The currently available insulin formulations are classified based on their onset/duration of action into rapid-acting, regular, intermediate-acting, long-acting, premixed regular/intermediate-acting, premixed rapid-acting/intermediate-acting, and rapid- and long-acting insulin combination formulations. Long–acting insulin formulations are used to supplement basal insulin secretion, whereas rapid–acting insulin formulations are used to supplement bolus insulin secretion. Whereas insulin therapy is associated with hypoglycemia, long–acting insulin formulations are less likely to lead to hypoglycemia compared with the other insulin formulations.

**Conclusions**

To prevent the onset and progression of diabetic complications, it is important to achieve better glycemic control without causing hypoglycemia in elderly patients with T2DM, who are more likely to develop hypoglycemia due to sulfonylureas, lactic acidosis due to biguanides, edema and heart failure due to thiazolidinediones, and ileus due to α-glucosidase inhibitors. Therefore, these drugs must be initially administered in lower doses. Attention should be paid especially in elderly patients who are at a higher risk for long–lasting hypoglycemia, and the choice of drugs, including their dosages, must be determined with circumspection in this patient population.

**Conflict of interest statement**

The author declares that they have no conflict of interest.

**Ethics policy**

This article does not contain any studies with human or animal subjects that were performed by the author.

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