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Management of Type 2 Diabetes Mellitus in Older Adults

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In the near future, the majority of patients with diabetes will be adults aged 65 or older. Unlike young adults with diabetes, elderly diabetic people may be affected by a variety of comorbid conditions such as depression, cognitive impairment, muscle weakness (sarcopenia), falls and fractures, and physical frailty. These geriatric syndromes should be considered in the establishment of treatment goals in older adults with diabetes. Although there are several guidelines for the management of diabetes, only a few are specifically designed for the elderly with diabetes. In this review, we present specific conditions of elderly diabetes which should be taken into account in the management of diabetes in older adults. We also present advantages and disadvantages of various glucose-lowering agents that should be considered when choosing a proper regimen for older adults with diabetes.

Keywords: Diabetes mellitus, type 2; Elderly diabetes; Geriatric syndrome; Sarcopenia

INTRODUCTION

The number of older adults with diabetes is rapidly increasing worldwide due to increased life span and a high prevalence of diabetes in the elderly. In many countries, the prevalence of diabetes is getting higher as a function of age. In Korea, one in every four adults aged 65 years and older had a diagnosis of diabetes in 2010 (Fig. 1) [1]. This figure is similar to the prevalence found in other countries. For instance, in the United States, among older adults aged ≥65 years, 10.9 million people (26.9%) had diabetes in 2010 [2].

Diabetes mellitus is a major cause of adverse health outcomes in older adults. In addition to well recognized microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary heart disease, cerebrovascular disease, peripheral artery disease) complications, older adults with diabetes may also suffer from devastating conditions such as depression, cognitive impairment, muscle weakness (sarcopenia), falls and fractures, and physical frailty [3-6]. These conditions should be classified as a third category of diabetic complications in older adults with diabetes, but until recently, it has been underappreciated. Primary care givers should be aware of these functional problems in older adults with diabetes.

Although there are several guidelines for the management of diabetes in general [3,7], only a few are specifically designed for older adults with diabetes [4,6]. In this review, we present specific conditions of elderly diabetes which should be taken into account to achieve treatment goals in older adults with diabetes. We also present the pros and cons of various anti-hyperglycemic agents that should be considered in older adults with diabetes.

PHYSICAL FRAILTY IN OLDER ADULTS WITH DIABETES

Physical disability

In older adults with diabetes, risks of disabilities related to mobility and daily tasks are increased by two-fold over those with-

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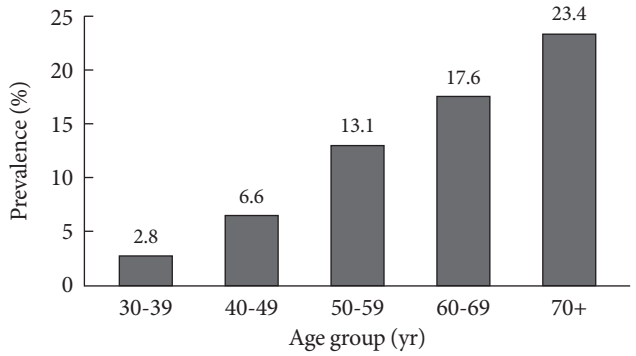

Fig. 1. Prevalence of diabetes mellitus according to age group among Korean adults in 2010. Data from Ministry for Health, Welfare and Family Affairs: The Fifth Korea National Health and Nutrition Examination Survey (KNHANES V-1) [1].

out diabetes [5]. In the United States, approximately 25% of older adults with diabetes are unable to walk one-quarter of a mile, climb 10 stairs, or do housework, and about 50% have difficulty performing these tasks [2]. In overweight or obese adults with type 2 diabetes, an intensive lifestyle intervention aiming at a minimum of a 7% decrease in weight and 175 minutes per week physical activity showed a relative reduction of 48% in the risk of loss of mobility [8]. Both weight loss and improved fitness were significant mediators for the prevention of mobility limitations. Apart from intensive lifestyle intervention, better glycemic control may improve both short-term and long-term maintenance of lower extremity function in older adults with diabetes [9].

Muscle weakness (Sarcopenia)

We have observed that older adults with type 2 diabetes have an altered body composition, low skeletal muscle strength, and poor muscle quality [10]. Furthermore, older adults with diabetes experience accelerated loss of lower extremity strength and muscle quality, as well as skeletal muscle mass [11,12]. Recently, these findings have been confirmed in the InCHIANTI study, which revealed that in older adults, diabetes is associated with reduced muscle strength and worse muscle quality [13]. These impairments in muscle function are important contributors to physical limitations related to diabetes in older adults.

Falls and fractures

Falls are common occurrences in elderly people and often result in serious injury and loss of independent living. Older adults with diabetes are particularly vulnerable to falls and related complications. In the study of osteoporotic fractures, older women with diabetes were reported to have an increased risk of recurrent falls [14]. In non-insulin treated patients, an age adjusted odds ratio for more than one fall per year was 1.67 (95% confidence interval [CI], 1.37 to 2.07), while in insulin-treated patients, it was 2.78 (95% CI, 1.82 to 4.24). Diabetes is also a powerful independent predictor of falls in older adults with disability [15].

Diabetes increases not only the risk of falls, but also the risk of fractures [16]. Increased fracture risk in type 2 diabetes is a paradoxical phenomenon because men and women with type 2 diabetes typically have normal to high bone mineral density [17,18]. Altered body composition and microvascular complications, including retinopathy, peripheral and autonomic neuropathy, hypoglycemia, and use of medications, particularly thiazolidinediones, are all related with increased risk of fractures in older adults with diabetes.

MENTAL HEALTH IN OLDER ADULTS WITH DIABETES

Cognitive dysfunction

Progressive cognitive decline and dementia are commonly observed in older adults with diabetes. According to a recent comprehensive meta-analysis, the aggregate relative risk of Alzheimer's disease for people with diabetes was 1.5 (95% CI, 1.2 to 1.8), and that of vascular dementia in patients with diabetes was 2.5 (95% CI, 2.1 to 3.0). The quantitative meta-analysis showed that diabetes was a risk factor for incident dementia and mild cognitive impairment [19]. Although it is less clear which factors account for the increased risk of dementia in diabetes, hypertension, hypercholesterolemia, diabetes duration, glycemic control, medication use, and genetic factors such as the *APOE* ε4 allele are all involved in the association between type 2 diabetes and dementia. Cognitive impairment in older adults with diabetes is known to affect diabetes self-management. Furthermore, older adults with diabetes are more likely to experience treatment-related complications. For example, elderly diabetics with cognitive impairment are at three times higher risk of severe hypoglycemia requiring health services [20]. They are also at increased risk of major cardiovascular events and death [21].

Depression

Depression is highly prevalent in older adults with diabetes.

Approximately 30% of people with diabetes have depressive symptomatology, 10% have major depression, and recent studies have shown that people with diabetes have two-fold increased odds of depression compared with individuals without diabetes [22-25]. The coexistence of diabetes and major depression is associated with increased health care use, increased health care costs, and adverse health outcomes for diabetes [24,26]. Furthermore, depression is associated with hyperglycemia and an increased risk for diabetic complications, and relief of depression is associated with improved glycemic control. Depression is also a major contributor to functional disability and quality of life. Functional disability in depressed patients is thought to result from decreased physical activity, decreased likelihood of seeking medical care, and increased susceptibility to disease [22,27]. Healthcare providers should be aware of the frequent coexistence of psychiatric conditions, such as depression or other psychiatric conditions, in elderly patients with diabetes. It is important to screen all diabetic elderly patients for mental health issues as these may interfere with self-care and the overall management of diabetes. Recognition and management of psychiatric disorders will help to optimize diabetes management. Good diabetes control can also reduce mental health complications in these patients [28].

TREATMENT GOALS IN OLDER ADULTS WITH DIABETES

The goals of diabetes management in older adults should be set according to the motivation, combined diseases, presence of complications, resources, support system, and life expectancy of each individual patient [7]. Most previous guidelines have failed to provide any specific recommendation for older adults with diabetes. The California Healthcare Foundation/American Geriatric Society Panel on Improving Care for Elders with Diabetes suggested that a reasonable goal for hemoglobin A1c (HbA1c) in relatively healthy elderly with good functional status should be 7% or lower. For frail adults, persons with life expectancy of less than 5 years, and others in whom the risks of intensive glycemic control appear to outweigh the benefits, a less stringent target of 8% was recommended [4].

It is less likely that the use of intensive therapy to target near normoglycemia (HbA1c <6.0%) will show benefits among older adults with diabetes. Elderly diabetics may have long duration of diabetes, previous history of cardiovascular diseases, or multiple cardiovascular risk factors, including hypertension, dyslipidemia, and many other comorbid conditions. All of the aforementioned conditions limit the benefits of intensive therapy in older adults with diabetes. On the contrary, as demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive management of hyperglycemia targeting HbA1c <6% may increase death from any cause (hazard ratio [HR], 1.19; 1.03 to 1.38, $P=0.02$) and death from cardiovascular causes (HR, 1.29; 1.04 to 1.60, $P=0.02$) [29,30]. Similarly, the Veterans Affairs Diabetes Trial (VADT) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial failed to show benefits in cardiovascular endpoints [31,32]. Therefore, intensive management targeting normoglycemia should be avoided in older adults. At a minimum, intensive control should be performed with great caution in older adults with diabetes.

GLUCOSE-LOWERING AGENTS IN OLDER ADULTS WITH DIABETES

In older adults with diabetes, the choice of anti-hyperglycemic agents should be based not only on efficacy, but drug safety (Table 1). Older adults with diabetes are at increased risk for adverse events from comorbid conditions and polypharmacy. They are also more likely to be decompensated by an insult from adverse effects of various anti-hyperglycemic agents. For instance, hypoglycemia may result in serious damage from consequent falls and/or fractures. Mild fluid retention induced by thiazolinediones may exaggerate underlying heart failure. Hepatic dysfunction and/or renal impairments in older adults may limit the use of many glucose-lowering agents.

Metformin

Metformin is currently recommended as the first line drug therapy for the management of diabetes in many guidelines because of proven effectiveness in lowering blood glucose, a relatively low risk of hypoglycemia, and low cost [33]. However, its use is often limited in older adults with diabetes because of comorbid conditions such as chronic renal insufficiency and heart failure. These conditions may increase the risk of lactic acidosis, a very serious adverse event associated with metformin. Metformin should not be given to men with elevated serum creatinine ≥1.5 mg/dL, and women with serum creatinine ≥1.4 mg/dL, or those with estimated glomerular filtra-

Table 1. Glucose-lowering effects, advantages, and disadvantages of various glucose-lowering agents in older adults with type 2 diabetes

	A1c lowering effect, %[a]	Advantages	Disadvantages
Metformin	1.0-2.0	Proven effectiveness as the first-line therapy Low risk of hypoglycemia Neutral effect on weight Long-term clinical experiences Low cost	Contraindicated when serum creatinine ≥1.5 mg/dL in men or ≥1.4 mg/dL in women, liver failure, and advanced heart failure GI side effects may cause poor appetite and malnutrition Concerns of vitamin B12 and folate deficiency
Sulfonylureas	1.0-2.0	Proven glucose lowering efficacy Long-term clinical experiences Relatively low cost	Frequent hypoglycemia Weight gain
Meglitinides	0.5-1.5	Rapid onset of action time Flexible dosing for those with irregular eating habits	Hypoglycemia Weight gain Frequent dosing Relatively high cost
DPP-4 inhibitors	0.5-0.8	Low risk of hypoglycemia Weight neutrality	Limited efficacy: only mild to moderate lowering of A1c by 0.5-0.8% Relatively high cost Limited long-term data
Alpha glucosidase inhibitors	0.5-0.8	Effectively reduce postprandial glucose No hypoglycemia	Frequent GI side effects Frequent dosing Relatively high cost
Thiazolidinediones	0.5-1.4	Reduce insulin resistance Durable effects on glycemic control Low risk of hypoglycemia	Weight gain Fluid retention, which may exacerbate underlying heart failure Increased risk of bone fractures Concerns of bladder cancer
GLP-1 receptor agonists	0.5-1.0	Low risk of hypoglycemia Weight reduction (beneficial in obese patients)	Relatively high cost Need a parenteral injection GI side effects may not be tolerated in some older patients High cost Limited long-term experience
Insulin	1.5-3.5	Proven effectiveness No dose limitation	Need a parenteral injection Frequent hypoglycemia Weight gain Need glucose monitoring and adjusting the dose accordingly Require patient's executive functioning

GI, gastrointestinal; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
[a]Expected reduction in HbA1c when used as a monotherapy.

tion rate (eGFR) of less than 30 mL/min. The use of metformin should also be avoided in older adults with liver failure, acidosis, hypoxia, and dehydration. Metformin should be used cautiously in older adults with diabetes because its frequent gastrointestinal side effects such as diarrhea, nausea, vomiting, and flatulence may cause poor appetite, reduced calorie intake, and weight loss. Treatment with metformin may also be associated with vitamin B12 and folate deficiency [34,35].

Sulfonylureas

Sulfonylureas remain an effective treatment regimen to achieve blood glucose targets when used alone or in combination with other anti-hyperglycemic agents. They are most often used in combination with metformin. The most common adverse effect limiting its use is hypoglycemia, especially in older adults with impaired renal function, hepatic dysfunction, and those with poor oral intake. The consequence of hypoglycemia in older adults with diabetes is sometimes devastating, e.g., loss of consciousness, falling, fractures, and loss of independence

[36]. Sulfonylreas with a long half-life, such as chlorpropamide, should not be used in older adults. Glibenclamide (glyburide) should also be avoided in older adults with diabetes because of increased risk of hypoglycemia. In older adults, sulfonylureas should be started with the minimal dose and titrated gradually based on blood glucose monitoring. When hypoglycemia appears, the dose of sulfonylurea should be reduced or it can be changed with the other insulin secretagogues with short duration of action, such as meglitinides. Alternatively, a dipeptidyl peptidase-4 (DPP-4) inhibitor can be used when a sulfonylurea may pose an unacceptable hypoglycemia risk in older adults with diabetes.

Meglitinides

This class of oral antidiabetic agents has a rapid onset time and relatively short half-life. The pharmacokinetic characteristics of meglitinides have the advantage of controlling postprandial hyperglycemia and reducing the risk of hypoglycemia [37]. Therefore, meglitinides can be used preferentially in older adults with diabetes with reduced renal function or those experiencing troublesome hypoglycemia with sulfonylureas. Although some studies report that the frequency of hypoglycemia is less common and the severity of hypoglycemia is mild to moderate compared to sulfonylureas, meglitinides are also associated with hypoglycemia. The need for frequent dosing and relatively high cost of the drug limits its wide usage and it is recommended to be used only in selected cases.

Incretins

Incretins (glucose-dependent insulinotropic polypeptide [GIP] and glucagon-like peptide-1 [GLP-1]) are hormones secreted from intestinal endocrine cells that stimulate insulin secretion and suppress postprandial glucagon secretion in a glucose-dependent manner. As evidences on efficacy and safety of GLP-1 receptor agonists and DPP-4 inhibitors have been accumulated, incretin-based therapy is becoming a cornerstone in modern diabetes management. It can be a good choice for older adults with diabetes because of its proven efficacy, low risk of hypoglycemia, fairly good tolerability and benefits in weight management.

GLP-1 receptor agonists

There have been many studies demonstrating the efficacy and side effects of GLP-1 receptor agonists, including exenatide and liraglutide, but none are specifically designed for older adults with diabetes. However, there are no differences in the efficacy and safety profile between elderly and younger patients [38]. More studies targeting older diabetic patients are needed.

DPP-4 inhibitors

DPP-4 inhibitors enhance the action of endogenous active GLP-1 and GIP by blocking its degradation by the enzyme DPP-4. This class of drugs seems to have advantages over sulfonylureas in older adults with diabetes for many reasons. The risk of hypoglycemia is low because of its glucose dependent mechanism of action. The safety profile of DPP-4 inhibitors is fairly good with few gastrointestinal side effects and weight neutrality. Recently, several clinical trials have shown the benefits of DPP-4 inhibitors in older adults with diabetes. Vildagliptin 100 mg daily resulted in better glycemic control, tolerability, and fewer adverse events compared with metformin 1,500 mg daily in drug-naive elderly patients with type 2 diabetes (mean age of 71 years with 3 years of diabetes duration) [39]. Vildagliptin is effective and well-tolerated in type 2 diabetic patients aged 75 years or older (mean age, 77 years) [40]. Sitagliptin also provides similar glycemic improvement with less hypoglycemia in the elderly with type 2 diabetes compared to sulfonylurea [41]. In older adults with type 2 diabetes, reductions in HbA1c after treatment with a DPP-4 inhibitor were not different from those in younger patients. Treatment with DPP-4 inhibitors in older diabetic adults was associated with a low risk of hypoglycemia, and these agents were weight neutral [42].

Thiazolidinediones (TZDs)

TZDs act as a peroxisome proliferator-activated receptor γ (PPAR-γ) ligand that improves insulin sensitivity in skeletal muscle and reduces hepatic glucose production in the liver. This class of drugs, including pioglitazone and rosiglitazone, does not increase the risk of hypoglycemia and has more durable action controlling hyperglycemia than sulfonylureas and metformin. However, rosiglitazone was withdrawn from the market due to concerns of the increased risk of myocardial infarction. Another agent in this class, pioglitazone, has recently been reported to be associated with increased risk of bladder cancer [43]. Long term use of pioglitazone for more than 24 months increased the risk of bladder cancer by two-fold (rate ratio, 1.99; 1.14 to 3.45) [44]. Other well identified adverse effects of TZDs include weight gain and fluid retention leading

to edema. Therefore, TZDs should not be used in patients with heart failure New York Heart Association (NYHA) class III or IV. TZDs are also associated with bone loss and increased risk of bone fractures, particularly in elderly women [45,46]. They are not recommended for use in older adults with preexisting osteoporosis. When TZDs are prescribed in older adults with low bone mass (osteopenia), changes in bone density should be closely monitored.

Alpha-glucose inhibitors (AGIs)

AGIs delay the rate of carbohydrate absorption by inhibiting intestinal mucosal enzyme (α-glucosidase) which is essential to converting complex polysaccharides into monosaccharides. The most frequently observed side effects include abdominal bloating, flatulence, and diarrhea, which may lead to patient nonadherence. There are controversial results regarding AGIs' effect on incretins, including GLP-1 and GIP. Some studies have shown that incretins are increased after the administration of AGIs [47,48], and other studies have failed to show a positive effect on incretins [49]. In older adults, clinical use of AGIs is limited by gastrointestinal side effects, frequent dosing, and the relatively high cost of drugs.

Insulin

Insulin is the most effective anti-hyperglycemic agent with a glucose-lowering effect of HbA1c reduction by 1.5% to 3.5%. Due to the progressive decline of β-cell function with increasing age, insulin replacement therapy is frequently required in older adults with type 2 diabetes with long duration of disease. However, there are many barriers to appropriate insulin use in elderly with diabetes. The most common obstacles are concern about hypoglycemia and complex nature of insulin administration. Multiple comorbid conditions in older adults with diabetes, e.g., impaired vision, poor physical function, and/or cognitive impairment, make it difficult to perform self-injection of insulin and also self-monitoring of glucose. In these situations, external resources, including family support and care givers, should be evaluated and insulin regimens need to be simplified and modified according to patient resources.

Long-acting basal insulin analogs (insulin glargine and detemir) are preferred in older adults with diabetes because these agents are relatively easy to titrate and have a decreased risk of hypoglycemia compared to NPH and regular insulin [50]. Long-acting insulins can be used either as monotherapy or in combination with metformin and/or sulfonylureas [51]. When metformin and/or sulfonylureas have been previously given to patients, this regimen is generally maintained when basal insulin is initiated and titrated.

If the glycemic goal is not achieved by basal insulin alone or in combination with oral antidiabetic agents and the patient can handle multiple injections, then more complex insulin regimens can be used in older adults with diabetes. Rapid-acting insulin analogues (e.g., insulin lispro, aspart, and glulisine) can be given before a main meal or before breakfast as a "basal-plus" regimen. Alternatively, instead of adding rapid-acting insulin, pre-mixed insulin can be given twice daily. In both cases, insulin therapy can be intensified to a "basal-bolus" regimen, involving the addition of premeal rapid-acting insulin at each meal to ongoing basal insulin [7].

CONCLUSIONS

In the near future, the majority of patients with diabetes will be adults aged 65 or older. Health problems in older adults with diabetes range from major complications of diabetes including cardiovascular disease, renal failure, blindness, to various conditions causing functional disability, such as sarcopenia, falls, fractures, cognitive impairment, depression, and physical frailty. Health care providers should evaluate and manage common geriatric syndromes in older adults with diabetes. The goals of diabetes management in older adults should be set differently in each individual patient. The choice of anti-hyperglycemic agents should be based not only on efficacy, but drug safety. Special attention needs to be focused on adverse effects, particularly hypoglycemia.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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