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MINIREVIEWS

Treatment of type 2 diabetes mellitus in the elderly

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Abstract

The prevalence of type 2 diabetes is expected to increase gradually with the prolongation of population aging and life expectancy. In addition to macrovascular and microvascular complications of elderly patients of diabetes mellitus, geriatric syndromes such as cognitive impairment, depression, urinary incontinence, falling and polypharmacy are also accompanied by aging. Individual functional status in the elderly shows heterogeneity so that in these patients, there are many unanswered questions about the management of diabetes treatment. The goals of diabetes treatment in elderly patients include hyperglycemia and risk factors, as in younger patients. comorbid diseases and functional limitations of individuals should be taken into consideration when setting treatment targets. Thus, treatment should be individualized. In the treatment of diabetes in vulnerable elderly patients, hypoglycemia, hypotension, and drug interactions due to multiple drug use should be avoided. Since it also affects the ability to self-care in these patients, management of other concurrent medical conditions is also important.

Key words: Diabetes mellitus; Oral antidiabetic drugs; Insulin; Elderly

Core tip: Diabetes mellitus (DM) is one of the most common lifelong chronic diseases in the world and its ratio is increasing by aging population. Elderly patients with type 2 DM have an increased risk for coronary heart disease, stroke and vascular diseases. While determining the treatment target and treatment options in elderly individuals, the functional capacity of the individual, comorbid diseases and treatment compliance should be evaluated together.

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INTRODUCTION

The prevalence of type 2 diabetes is expected to increase gradually with the prolongation of population

aging and life expectancy. In addition to macrovascular and microvascular complications of elderly patients of diabetes mellitus (DM), geriatric syndromes such as cognitive impairment, depression, urinary incontinence, falling, polypharmacy and sarcopenia are also accompanied by aging[1]. Sarcopenia is characterised by a progressive decline in skeletal muscle mass and that is the reason for low muscle strength and impaired physical performance[2]. Elderly (adults over age 65 years) individuals with type 2 DM have a great risk for sarcopenia and physical disability[3]. The mechanism responsible for loss of musclein type 2 DM is uncertain. Changes in skeletal muscle protein turnover may be involved in such alterations in type 2 DM and it can play an essential rol in this pathogenesis[4,5]. There is also a small amount of studies involving elderly diabetic patients, one of the major reason for that is individual functional status in the elderly shows heterogeneity. The physiological changes that develop with aging make it more difficult than studies for to the young age group. As a result, there are many unanswered questions about the management of diabetes treatment in elderly patients. The "patient-centered" treatment regime in the geriatric age group is gaining importance for this reason.

Incidence

Type 2 diabetes is a common health care problem on modern world and it is increasing day by day with the prolongation of life span. In a study conducted in the United States, it was found that the prevalence of type 2 diabetes increased from 16% to 23% between 1995 and 2004[6]. According to the current data, in the United States, among adults over 65 years of age 22% to 33% of them are diagnosed with diabetes. It is predictable that the incidence of diabetes could double in the next 20 years. According to another projection; It is estimated that this increase will be about 4.5 times between 2005 and 2050 in individuals aged 65 and over[1].

Diabetic characteristics in the elderly population

Glucose intolerance increases progressively by aging and the characteristic feature of diabetes in elderly patients is especially postprandial hyperglycemia. Decrease in beta-cell-compensating capacity with advancing age, leads to insulin resistance and it appears as a postprandial hyperglycaemia in the elderly[7]. Therefore, the prevalence varies according to the tests used during diagnosis on elderly patients. One third of the individuals who are tested with A1C or fasting plasma glucose (FPG) are cannot get a diagnosis[8].

The incidence of DM increases with aging. As a result, adults may be diagnosed incidentally after the age of 65, or may have had a diabetes diagnosis in middle age or earlier onset. Having different demographic and clinical characteristics of these two groups may cause confusion caused by the setting of the general treatment recommendations. Age-related DM is characterized by lower A1C and the use of less insulin, with frequent occurrence in non-Hispanic whites. In comparison adults with diabetes diagnosed in middle age, the retinopathy story is more prominent in late-onset diabetic cases, and interestingly there is no difference in prevalence of cardiovascular disease (CVD) or peripheral neuropathy according to age at onset[9]. In diabetic adults increased development risk of lower extremity amputation, myocardial infarction (MI), impaired vision and end-stage renal disease. Patients over 75 years of age have a higher risk of developing multiple complications than the age group of 65-74[10].

Older adults are at higher risk for developing type 2 diabetes because of the combined effects of increased insulin resistance and pancreatic islet dysfunction.

Economic burden

The burden of treatment of older diabetic patients on country economy is quite high. According to the analysis made in the United States in 2010; More than 14 million patients whose age 65 and over are hospitalized annually and approximately one-third of them are diabetic[11]. Again according to United States data, about $245 million is spent yearly on diabetes patients, of which $176 million is direct medical costs, while $69 million is the loss of production and mortality[12]. In addition, 59% portion of the annual treatment costs have been made for the elderly diabetic individuals. Most of the expenditures are caused by hospital admissions, home care and prescripted drugs. These extreme expenditures vary from about $23900 to $40900 per person, depending on gender and age[13].

TREATMENT TARGETS

The goals of diabetes treatment in elderly patients include hyperglycemia and risk factors, as in younger patients. However, the elderly patient group has a heterogeneous structure, some of them are self-caring independently, while the others need care in a nursing home. For this reason, comorbid diseases and functional limitations of individuals should be taken into consideration when setting treatment targets. Thus, treatment should be individualized.

There is limited number of studies investigating the effect of glucose-lowering therapy on cardiovascular complications and mortality. For the reason that the elderly diabetic patient population is not included in clinical trials, we do not have sufficient data on glucose control.

In the United Kingdom Prospective Diabetes Study (UKPDS), in which the effect of glycemic control on microvascular complications is examined, new diagnoses of middle-aged diabetic patients were taken and > 65 years of age were excluded from the study[14]. At the end of the study, there was a statistically significant decrease in both mortality and cardiovascular events in the group ensured early glycemic control. Also observed that microvascular beneficial effects continue after the

study.

After the UKPDS results were published, three important randomized controlled trials (ACCORD trial, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT) are planned. These studies are designed to examine the effect of glycemic control on CVD events in middle-aged and older patients with type 2 diabetes. The ACCORD trial was terminated approximately 3 years after due to deaths onthe strict glycemic control group[15]. MI, stroke and cardiovascular death were not significantly reduced in primary combined outcomes. In subgroup analyzes, hypoglycemia and other side effects were more commonly detected in elderly participants. In the ADVANCE trial, there was no increased risk of mortality in the strict glucose control group after 5 years of follow-up. When study data were evaluated, there was no statistically significant decrease in cardiovascular risks in the group receiving intensive treatment, however, a significant decrease in the incidence of nephropathy was found[16]. In the VADT trial, there was no statistically significant effect on major cardiovascular events or mortality in the intensive glucose control group after 5 years of follow-up, as well as there wasn't any reversible effect on albuminuria progression. In the intensive group, beneficial effects on mortality were observed in 15 year follow-ups, but higher mortality was found in this group over 20 years[17].

These studies are important in assessing the benefits and risks of strict glycemic control in elderly patients. For this reason, when glycemic control targets are determined, treatment should be individualized considering the life expectancy as well as the chronological age of the patient.

In the treatment of diabetes in vulnerable elderly patients, hypoglycemia, hypotension, and drug interactions due to multiple drug use should be avoided. Since it also affects the ability to self-care in these patients, management of other concurrent medical conditions is also important.

Glycemic targets

In elderly patients receiving medication, there are few data that address the most appropriate glycemic targets. The goals to be determined in the management of glycemic control and risk factors should be based on both the general health status and the predicted life span of the individual. A proper target for A1C in elderly patients with a life expectancy of more than 10 years may vary according to the above factors, the risks of patient-specific hypoglycemia and compliance with treatment regimens[18].

Despite the lack of long-term clinical trials with elderly individuals, patients with life expectancy more than 10 years and drug treated the A1C target should be < 7.5% (58.5 mmol/mol).

Drug treated elderly adults with medically-functional comorbidities and have less than 10 years of life expectancy should have a slightly higher glycemic target [A1C $\leqslant$ 8.0, fasting and pre-prandial glucose should be between 160 and 170 mg/dL (8.9 to 9.4 mmol/L)].

Individualized targets for older adults may be even higher (A1C < 8.5%). The aim of the treatment is to protect the quality of life, prevent hypoglycemia and related complications. Eight point five percent for A1C value and 200 mg/dL for average glucose (11.1 mmol L) should be targeted.

These targets are consistent with the American Geriatrics Association, the American Diabetes Association, the International Diabetes Federation and the European Diabetes Working Group.

In addition, when A1C levels are assessed in elderly patients, accompanying diseases or metabolic conditions should be considered. These include anemia, diseases affecting the erythrocyte life, chronic kidney disease, chronic liver disease, recent blood transfusion or erythropoietin infusion, acute infections and hospitalization. Initial therapy in elderly patients, the same as in younger patients; regulation of nutrition, physical activity, improvement on metabolic control and prevention from complications.

Lifestyle changes

Counseling should be provided on all elderly diabetic patient lifestyle changes (exercise, diet, behavioral changes, and weight loss in patients who need it). In elderly diabetic group response to the lifestyle changes (low fat diet and 150 min/wk exercise) were found to be higher than the young diabetic age group according to the diabetes protection program (DPP)[19].

Physical activity: Elderly diabetic patients should be guided to activities according to their functional capacities. Prior to physical activity, high-risk, symptomatic individuals with coronary artery disease should be evaluated with electrocardiograms and/or cardiac tests. Functionally independent individuals are offered a moderate aerobic activity of at least 5 d for 30 min each week. Except this, patients with high risk of falling should be directed to physiotherapists for balance and muscle strengthening exercises before workout.

Medical nutrition therapy: All elderly diabetic patients should be given medical nutrition education and treatment should be adjusted to their individual needs. When preparing the eating plan, age-related person-specific differences (deterioration in taste, additional illnesses, dietary restrictions, impaired gastrointestinal function, reduced ability to shop, and reduced food preparation capacity) must be considered.

Medical therapy

In elderly diabetic patients, lifestyle changes is recommended with metformin for treatment, primarily because of the risk of hypoglycemia, unless there is a contraindication (renal failure and unstable/acute heart failure)[20]. However, patients with comorbid disease,

multiple drug use, or HbA1c levels close to target levels should be monitored for 3-6 mo with lifestyle changes before initiation of metformin therapy.

At the time of diagnosis patients whose HbA1c level was > 9% (74.9 mmol/mol), FPG level was > 250 mg/dL (13.9 mmol/L), randomly observed glucose value > 300 mg/dL (16.7 mmol /L) or who have ketonuria insulin should be selected as initial theraphy.

There is a small amount of research on the use of medication in elderly patients. All hypoglycemic drugs and insulins can be safely used in elderly patients, with some restrictions. In general, those with low risk of hypoglycemia should be preferred as oral or injected agents.

Pharmacological treatment should be regulated according to the person's abilities and comorbodities. Elderly patients should be treated with the principle of "start low and go slow". Oral antidiabetic drugs and insulin are used in the treatment of diabetes in the elderly.

INSULIN SENSITIZER DRUGS

Metformin

Metformin decreases hepatic glucose production by inhibiting gluconeogenesis in the liver. In many elderly patients, metformin is chosen as the initial treatment. Low cost, positive effects on CVDs, low risk of hypoglycemia the anti-aging effects makes metformin an attractive choice for elderly patients[21]. The most important restricting factor of metformin treatment is glomerular filtration rate (GFR) and treatment can be started if GFR of the patient is > 30 mL/min. It is recommended to use a full dose in patients with GFR > 60 mL/min and a half dose (1000 mg/d) in patients with GFR 30-60 mL/min. Two other factors that limit metformin treatment in elderly patients are weight loss and gastrointestinal side effects. However, the treatment may be started at 500 mg/d and the gastrointestinal side effects may be minimized by slowly increasing the dose within weeks.

Elderly patients should also be used metformin cautiously as it may cause renal dysfunction or lactic acidosis. Patients using metformin should be warned for stopping medication if the use of iodine-containing contrast media is needed for any reason. In addition, evaluation of renal function tests every 3 to 6 mo is necessary.

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist drugs and these drugs regulate the transcription of genes that respond with PPAR activation[22]. These drugs are effective in increasing insulin sensitivity in peripheral tissues, primarily skeletal muscles. It is the group of drugs that can be preferred in the elderly who are not using the insulin treatment and that the sulfonylurea treatment is contraindicated. This drug group being able to be preferred in patients with impaired renal function, as well as low risk of hypoglycemia and has the greatest advantage to be well tolerated in elderly patients. Peripheral edema may develop in 4%-5% of patients during treatment, and is contraindicated in patients with class Ⅲ-Ⅳ congestive heart disease[23]. In addition to these, the most important disadvantages are: It can exacerbate ophthalmopathy, increase the risk of bone fracture, increase weight in combination with insulin therapy, cardiovascular events (fatal and nonfatal MI) and increase in bladder cancer. Patients with active bladder cancer or history, defining macroscopic hematuria or having complaints of hematuria, dysuria, pollakuria, waist and back pain during thiazolidinedione usage should be screened for bladder cancer before the onset of treatment[24]. Because of the disadvantages of them (congestive heart failure, risk for falls or fractures), their use is not recommended on elderly patients, however for the selected patients dosage should be started at the lowest dose and the duration of treatment should be kept as short as possible[25].

INSULIN RELEASING (SECRATOGOGUE) DRUGS

Sulfonylureas

Short-acting sulfonylureas (*e.g.*, glipizide) are recommended as initial therapy in patients with metformin therapy contraindicated or unable to tolerate it. Side effects such as hypoglycemia and weight gain should be considered in addition to glucose lowering effects, easy availability and low cost in the selection of sulfonylureas (SU). Glipizide, glyburide (glibenclamide), gliclazide and glimepiride are 2nd generation SUs and are more potent than 1st generation SU and have less side effects. Glyburide (glibenclamide) and glimepiride have a long half-life and are used in a single daily dose and reduce fasting glucose by inhibiting night hepatic glucose output and cause elevated risk of hypoglycemia[26]. The risk of hypoglycemia is increased especially in patients with renal insufficiency, elderly patients, multiple drug users, patients with dementia, heart failure and long-term diabetes[27].

In elderly patients, sulfonylurea-related hypoglycemia is variable. In general, from diabetic patients in hospital, hypoglycemia was more common in patients aged > 75 years, compared to groups aged 65-74 years. Admission to the hospital with the cause of severe hypoglycemia in the elderly is associated with greater health problems than admission with hyperglycemia, which suggests to have opportunities to improve health through rational drug selection in the elderly with diabetes[28]. Short-acting ones such as glipizide should be preferred if the SU treatment is planned to be given in the elderly. The initial regimen of glipizide 2.5 mg should be regulated as half an hour before breakfast, and if sufficient glycemic control

cannot be achieved within 2-4 wk, the dosage should be increased to 5-10 mg.

Meglitinides

Similar to sulphonylureas, act on pancreatic beta cells to increase the 1st phase of insulin secretion through ATP-dependent potassium channels through different receptors. The blood glucose lowering effect with fast onset and a short duration[29]. Especially the effects on postprandial hyperglycaemia are distinctive, so they are used just before meals. Use of just before each meal can cause discontinuation in the treatment of older adults with cognitive pathology[30]. The most important side effects, though not as obvious as SUs, are hypoglycemia and weight gain. The risk of hypoglycemia is more pronounced in older adults, especially those who skip meals. Repaglinide is metabolised from the liver, so it can be safely used in the elderly with renal insufficiency without need for dose adjustment. It is a good option as initial therapy in older patients with chronic renal failure who cannot tolerate metformin and SU treatment[31]. Also the repaglinidin's A1C lowering effect is higher than nateglidine.

ALPHA GLUCOSIDASE INHIBITORS

They function by inhibiting carbohydrate absorption by inhibiting the enzyme alpha-glucosidase in the small intestine. The drugs in this group are acarbose, miglitol and voglibose. It is advised to take it before every meal but it can be used at the time of meal with postprandial hyperglycemia (PPH) only because it affects PPH. The most important side effects are swelling, indigestion, diarrhea, reversible increase in liver enzymes and rarely iron deficiency anemia. Contraindications include inflammatory bowel disease, chronic ulceration, malabsorption, partial bowel obstruction and cirrhosis. In addition, treatment should be discontinued in patients with an eGFR of 25 mL/min[32].

INCRETIN BASED MEDICATIONS

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4I) is a member of a large family of enzymes responsible for the destruction of many GIS hormones, neuropeptides, chemokines and cytokines. In response to food-borne carbohydrates, they are secreted from small intestine's K and L cells. They increase pancreatic insulin secretion, slow down gastric emptying, and suppress the increased postprandial glucagon secretion[33]. DPP-4 inhibitors are an attractive treatment option for elderly diabetic patients due to the single daily dose, lack of risk for hypoglycemia and neutral effect on weight. The most important side effects are headache, nasopharyngitis, upper respiratory tract infection and acute pancreatitis. Creatinine clearance should be calculated before treatment in each patient and dose should be reduced if < 50 mL/min. For sitagliptin if Egfr < 30 mL/min for, it should preferably not be used and if the eGFR is between 30-50 mL/min, the dose should be reduced by 50%. If eGFR < 15 mL/min in vildagliptin, saxagliptin, and linagliptin, they should preferably not be used, but for Vildagliptin if eGFR between 30-60 mL/min or patient has dialyzed it can be used without dosage adjustment. For Alogliptin treatment, if the eGFR is 30-60 mL/min, the dose is reduced by 50%, whereas if the eGFR is < 30 mL/min, the dose is reduced by 75%.

In the study comparing glipizide and sitagliptin in elderly diabetic patients, A1C reduction was similar in both groups, but less hypoglycemic event was encountered in the alogliptin-receiving group[34]. In another study conducted by Scirica *et al*[35], the group receiving saxagliptin treatment in elderly diabetic patients was found to have a higher rate of hospitalization with cardiac insufficiency. On the other hand; a systemetic rewiew deduced that incretin-based treatment(agents) does not increase major adverse cardiovascular events[36]. The effects of the DPP-4 group drugs on the A1C lowering are insufficient. Therefore, monotherapy can be used in patients with A1C level close to the target value. They may also be added to metformin, SU and insulin therapy.

Incretinmimetics (glucagon like peptid-1 receptor agonists)

Glucagon like peptid-1 receptor (GLP-1) agonist drugs also target postprandial hyperglycemia and theirhypoglycemia risk is relatively low. However, nausea and weight loss are the most important side effects in vulnerable patients. Other negative features are that they are administered as injections, renal dose reduction and high treatment costs.

Studies have shown that at the end of the 24-wk follow-up period with liraglutide treatment, the decrease in fat mass and lipid profile, as well as the increase in glucose control and insulin sensitivity[37]. In another study about cardiovascular effects of liraglutide treatment, the incidence of non-fatal MI or nonfatal stroke due to cardiovascular causes was found to be lower in patients receiving liraglutide treatment compared to placebo[38].

In another study, the rate of cardiovascular death, non-fatal MI, or non-fatal stroke was found to be significantly lower in type 2 diabetes patients with semaglutide treatment compared to those who received placebo. This result confirms the noninferiority of semaglutidine[39].

Sodium glucose co-transporter 2 inhibitors = glucoretics

Although there isn't any long-term efficacy and safety data available, they may be preferred as treatment options in cases in which sufficient glycemic control is not achieved with dual oral agents such as metformin and SU. Sodium glucose co-transporter 2 inhibitors (SGLT2-I) is secreted in the proximal tubules and reabsorbs about 90% of the glucose load undergoing filtration. The effect of lowering the plasma glucose level and A1C level is limited by the filtered glucose load and osmotic diuresis, and also insulin independent and can be used in any stage of DM2. A1C is reduced by

0.5%-1%. Even though long-term efficacy is unknown, but it has been found that within 2 to 6 mo, it causes about 2 kg of loss, 2-4 mmHg decline in systolic blood pressure, and 1-2 mmHg decline in diastolic KB. It also has the advantages of lowering the level of uric acid and decreased albuminuria and also low risk for hypoglycemia[40]. The most important side effects were increased genital-mycotic infections (11% in females, 4% in males) and an elevated volume gap due to increase in urinary tract infections and diuretic effects[41].

When cardiovascular results of studies with these group drugs were evaluated, there was a significant decrease in the risk of cardiovascular events and cardiovascular caused mortality with Empagliflozin[42]. In the subgroup analysis of the same study, it was found that Empagliflozinhas renoprotectiveeffects and reduced the risk for development of renal complications[43]. The study of the concurrent use of DPP-4I and SGLT2-I treatment showed that monotherapy was more effective in patients treated with metformin, when a gliptin was added to gliflozin, it was determined that it had the effect of more glucose lowering than when a gliflozin was added to gliptin. The opinion at the end of the meta-analysis is that SGLT2I and DPP-4I can be used as an initial combination or as a gradual approach and combining two pharmacological options is safe and does not induce hypoglycemia[44]. Furthermore, when the sum of the evidence for the use of dapagliflozin is assessed, it has not been shown that there is a causal relationship between dapagliflozin and bladder cancer, which was previously proposed[45].

Should be used more carefully in elderly because for causing osmotic diuresis resulting dehydration, causing an increase in the frequency of genital and urinary system infections, weight loss, dose adjustment necessity in renal failure and lack of enough data on microvascular and cardiovascular outcomes.

INSULIN THERAPY

In the elderly with poor glycemic control, HbA1c level > 9% (74.9 mmol/mol), FPG level > 250 mg/dL (13.9 mmol/L), randomized glucose value > 300 mg/dL or patients with ketonuria, insulin should be selected as initial therapy. When starting insulin therapy in elderly patients, it is important to have general health status, ability to make insulin, to measure blood sugar, to understand hypoglycemia and capacity to treat it. In the study of geriatric patients using basal insulin and OAD, treatment-related satisfaction surveys and post-12-wk follow-up in the insulin treatment group showed significant improvement in the geriatric depression scale (SOURCE). In another study, geriatric patients were divided into OAD treatment with basal insulin addition and elevated OAD dosage group, and 24-mo follow-up revealed a lower frequency of hypoglycemia in the basal insulin group (SOURCE). In a randomized controlled trial in long-term care patients, basal insulin was added to a group and OAD added to another group and glycemic control and development of hypoglycemia were evaluated and no significant difference was detected. When the ready mixed insulins are evaluated, they are more effective for the control of postprandial glycaemia, but they are more useful for the patients who live in the nursing home, who eat regular meals.

New oral glucose-lowering agents are less likely to have all-cause mortality, CVD, and severe hypoglycemia when compared to insulin. Dapagliflozin has both decreased mortality due to all causes and reduced CVD risk, while DPP-4i has been found to be weaker in decrease of all cases due to mortality[46].

Elderly patients have their own nutritional needs.Along with the increased age, the taste and odor sensations diminishes, as well as changes in the threshold of thirst. For this reason, the balance between pre-meal insulin and oral food intake should be well established in elderly patients. Insulin dose reduction should be done according to the amount of carbohydrates taken at meals, for example if half of the meal is consumed, insulin will be reduced by 50%, insulin will not be administered or 25% can be administered to patients who consume less than that or may skip meals due to a medical intervention. In addition, patients with enteral or parenteral nutrition should be monitored for glucose at 4-6 h intervals to avoid hypo-hyperglycaemia[47].

CONCLUSION

When starting OAD or insulin therapy in the elderly, treatment regimens containing as simple and few drugs as possible should be administered, and drug therapy should not be initiated unless it is necessary and if necessary must start with low dose and dose increase should be done slowly. All patients should be evaluated with liver and kidney function tests before onset of treatment.

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