



Review

Approach Toward Diabetes Treatment in the Elderly

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Abstract

Concomitant diseases in elderly individuals with diabetes (renal failure, heart failure, ischemic heart disease, stroke, urinary incontinence, cognitive impairment, dementia, sarcopenia, and osteoporosis) make diabetes management difficult. Therefore, other comorbid conditions should be taken into account in elderly diabetics when considering a treatment approach. The use of oral antidiabetic agents in individuals older than 75 years may be limited. Although the diabetes treatment is not any different in healthy elderly patients, hypoglycemia is one of the most feared conditions, especially in the elderly. Therefore, metformin, DPP-IV inhibitors, and SGLT2 inhibitors should be considered in the first place with less risk of hypoglycemia. Low-dose sulfonylureas may also be used in selected cases. The use of new antidiabetic drugs, such as GLP-1 analogues and SGLT2 inhibitors, has strengthened our ability to cope with the risk of hypoglycemia and cardiovascular events, which are the two most important drawbacks in the treatment of elderly people with diabetes. Insulin treatment should be individualized, and the most rare injection regimens should be used. In case of failure of OAD, basal insulin should be added to the current treatment, and if necessary, a basal + plus regimen should be planned by adding bolus insulin 1/2/3 times per day to the meals. As a result, in elderly diabetics, an inadequate treatment or excessive treatment and individualizing the treatment should be the most appropriate approach.

Keywords: Antidiabetic therapy; diabetes; old age.

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As the average life expectancy is prolonged, the number of elderly people is increasing. It is estimated that the prevalence of diabetes worldwide will increase to 642 million by 2040, and the highest age-specific increase will be observed in the 60-79 age range. Today, 20% of people aged 70-79 are diabetics. The aging of the world population is one of the most important causes of the increase in diabetes prevalence because increasing age is a significant risk factor in the development of diabetes. A greater number of patients with type 2 diabetes (>90%) are seen in the elderly population. Both the insulin resistance and

beta cell dysfunction play a crucial role in its pathogenesis. Insulin resistance due to advanced age is related to adiposity, sarcopenia, and physical inactivity. In addition, LADA presented at advanced age and type 1 diabetics diagnosed at an early age reaching to old age are also diabetics in the elderly.

Other concomitant diseases and conditions caused by aging along with diabetes become more frequent with increasing life expectancy. Kidney failure, heart failure, ischemic heart disease stroke, urinary incontinence, cognitive disorder, dementia, sarcopenia, and osteoporosis are

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the main causes of diabetes management in the elderly. Therefore, a treatment approach should be considered in elderly diabetics also taking into account other comorbid conditions.^[1] In the light of all these developments, diabetes treatment has become the target of cardiovascular protection in addition to reducing blood sugar.

Physiopatological Changes In Elderly Diabetics

Although there is no evidence that the pathophysiology of elderly with type 2 diabetes is different from that of young people, the beta cell defect, which is accelerated by insulin resistance in advanced age, is more prominent. Therefore, postprandial hyperglycemia is more evident.

Nighttime hyperglycemia is not clear because the nocturnal peak of cortisol is weak in the elderly. There is a delay in the glucose absorption and a delay in hepatic glucose production suppression. LBM is associated with an increase in insulin resistance due to the decrease in body fat and increase in LBM.^[2]

Changes in the Signs and Symptoms of Diabetes in the Elderly

Physiological changes that take place with aging may alter the signs and symptoms of classical diabetes. Hyperglycemia symptoms may vary. Glucosuria may not be present because the renal glucosuria threshold increases with age. Polydipsia may not be present because of changes in the perception of thirst. Frequently, dry eye, dry mouth, confusion, urinary incontinence, or diabetes complications may be the first signs and symptoms.^[3]

In the elderly, dehydration should be kept in mind as a result of insensitivity to hunger and sometimes insensitivity to the feeling of satiety.

Nutrition Changes In Elderly Diabetics

In elderly diabetics, mealtimes may vary or may not be predictable. Diabetics who use insulin may not adapt to the meals. The incidence of malnutrition in elderly people with diabetes is increased. This is due to morbidities (infections, end-stage renal failure, or cancer), anorexia due to drugs, or excessive restriction of the diet. Subclinical vitamins and essential nutrient deficiencies may play a role in the impairment of cognitive functions.^[4]

Conditions From Age and Diagnosis Relations with Diseases

With increasing age, there is a decrease in the functional capacity, whereas falls, dementia, urinary incontinence, polypharmacy, resistant pain, and depression frequency increase.

Inadequacy in functional capacity: Diabetes increases the risk of not performing daily work 2–2.5 times.^[5] Difficulty in providing self-care, tremor, osteoarthritis, affective, and cognitive diseases require the help of someone else to make the diabetes treatment easier.

Dementia: The weight loss due to the insensitivity to the feeling of hunger in severe dementia and dehydration resulting from the insensitivity to satiety (if not corrected, nonketotic hyperosmolar state may occur) complicate diabetes management. Therefore, an annual screening is recommended in mild cognitive dysfunction and dementia diagnosis.

Frailty: In diabetic individuals, aging is faster, and in the presence of a large number of chronic diseases affecting multiple systems, frailty starts at an earlier age.^[5, 6] A decrease in the muscle and nerve function, decreased cardiopulmonary reserve, difficult movement, weakness in one hand, fatigue, more than five diseases, weight loss $\geq 5\%$ in 1 year or less have been determined. For this reason, sarcopenia should be evaluated in diabetics. Resistance exercises that increase the muscle strength should be recommended. Protein support should be given if necessary, and vitamin D and anabolic therapy are not recommended.^[7] Drugs that may cause sarcopenia should be reviewed, and metformin should be carefully administered because it may reduce the appetite and facilitate weight loss.

Urinary incontinence: Postmenopausal women aged 55–75 years have urinary incontinence in 52% cases, and severe incontinence in 15%. The weight loss through lifestyle changes (38.3%) can reduce urinary incontinence.^[8] The SGLT2 inhibitors should not be given to such diabetics.

Depression: Approximately 30% of patients with diabetes showed depressive symptoms, whereas only 5%–10% are present in those patients without diabetes.

Depression is 31% higher in the 70–79 age group.^[9] Depression leading to poor hygiene, anorexia, and noncompliance with drug therapy makes it difficult to treat diabetes in the elderly.

Goals of Glycemia in Elderly Diabetics and Monitoring

Different glycemia targets should be planned in older diabetics, considering the age, type of diabetes, duration, the frequency of hypoglycemia, comorbid conditions, and functional status. The most feared complication of hypoglycemia is that hypoglycemia-induced hospitalization exceeds hyperglycemia-induced hospitalization rates in elderly patients with diabetes.^[10]

According to the TEMD guideline, in healthy elderly patients who are functional and whose cognitive capacity is

normal and life expectancy long enough to benefit from treatment, A1c should be targeted to <7%, as in young people with diabetes.

In elderly diabetics who have multiple chronic diseases, mild to moderate cognitive impairment, and shortened life expectancy, A1c should target 7.1%–8%, fasting and pre-meal plasma glucose at 90–150 mg/dl, and overnight plasma glucose at 100–180 mg/dl.

Glycemic and metabolic targets should be kept more flexible in the elderly with advanced complications who have significant health problems, have a short life expectancy, are fragile, functional, or have a limited cognitive capacity. For these patients, A1C <8.5, fasting or pre-meal plasma glucose at 100–180 mg/dl and night plasma glucose at 110–200 mg/dl is recommended.^[12]

Nutritional Status and Treatment in Elderly Diabetics

The energy requirement in the elderly is 20%–30% lower due to a different body composition and less frequent and strenuous exercise. Aging is accompanied by many biological changes that may lead to nutritional deficiencies. These changes are related to taste, smell, and chewing, changes in the saliva flow, gastric acidity, changes in the hepatic and renal functions, multiple drug use, alcoholism, and difficulties in food preparation. The assessment should start with a nutritional history, including a psychosocial and environmental assessment.

Exercise in Elderly Diabetics

Physical activity, especially endurance exercises, is necessary to prevent muscle loss. Exercise prevents the decrease caused by aging in the maximal aerobic capacity and a decrease in atherosclerotic risk factors. A hundred and fifty minutes of moderate exercise (50% maximum heart rate) are recommended per week. If there are no contraindications, resistance exercises are recommended two times a week. Cardiac ischemia, musculoskeletal damage, the pres-

ence of neuropathy, and hypoglycemia (insulin or insulin secretagogue) should be considered.^[12]

Principles of Treatment in Elderly Diabetics

There are no large randomized controlled trials that examined the control of diabetes and its effects on vascular complications in the elderly (>75 years). Larger reductions in morbidity and mortality occur by controlling other cardiovascular risk factors rather than glycemic control alone. It is necessary consider the age limit for the antidiabetic drugs to be used (Table 1). There is serious evidence for the control of hypertension. Despite the benefits of primary protection, there is little evidence for lipid lowering and aspirin.

The screening of diabetes complications should be individualized. Treatments of hypertension and lipid should be individualized in addition to diabetes. Treatment of lipid and aspirin provides primary and secondary protection.

Influenza and conjugated pneumococcal vaccination also should not be forgotten.

Heart failure is a condition that should not be ignored in the treatment of diabetes. In recent years, drugs that reduce or increase the risk of heart failure have become important in the treatment of diabetes (Table 2).

The risk of fractures in the treatment of diabetes in the elderly should also be considered (Table 3).

The incidence of sarcopenia is high in the elderly. Sulfonylureas that may lead to sarcopenia should be considered (Table 4).

Metformin

Metformin is an indispensable first-line drug in the elderly as well. Its efficiency and tolerability are good. The risk of hypoglycemia is low, and its effect on weight is neutral or it leads to weight loss. Long-term randomized controlled tri-

Table 1. Safe age limits for antidiabetic drugs application in the elderly

Age and the treatment of antidiabetics	
Metformin	Not recommended for use after 80 years of age
Sulphonylureas, glinides	No age restrictions
Pioglitazones	Up to 75 years old
Sitagliptin, saxagliptin	Safe for 65–75 years
Vildagliptin	Safe for 75–84 years
GLP-1 A	Up to 75 years old
SGLT2 inhibitors	Up to 75 years old

Table 2. Correlation between heart failure and antidiabetic drugs

Antidiabetics and heart failure	
DECREASE OF RISK	INCREASE OF RISK
SGLT2 inhibitors	Glitazon (RECORD, PROactive)
(empagliflozin and canagliflozin)	
GLP-1 agonist (LEADER study) NS	Saxagliptin (SAVOR-TIMI53)

Table 3. Relationship between the fracture risk and antidiabetics

Fracture risk and OAD	
INCREASE IN FRACTURE RISK	DECREASE IN FRACTURE RISK
Sulphonylureas	DPP-IV Inhibitors
TZD	
SGLT2 Inhibitors	

Table 4. Relationship between sarcopenia and antidiabetics

Sarcopenia and the treatment of antidiabetics	
Metformin	Its effect is controversial/partially useful
TZD	Effective in animal models
Sulphonylureas, glinides	Triggers muscle atrophy
Incretins	The effect on sarcopenia is useful
SGLT2 inhibitors	No data
Insulin	No corrective effect on muscle atrophy in elderly

als, such as the UKPDS, have demonstrated that metformin has beneficial effects on specific complications of diabetes and on mortality and morbidity.

It has been suggested that metformin can protect the epigenetic modifying enzymes, such as histone acetyl transferase and histone methyl transferase via AMP-kinase enzyme, and thus protect against cancer, cardiovascular diseases, a decrease in cognitive functions, and provide anti-aging effects.^[13] The effects on heart failure and atherosclerotic cardiovascular disease and diabetic renal disease progression are neutral. Renal dysfunction eGFR is 30–45 ml/min in half dose) and eGFR is contraindicated in <30 ml/min. Nonobese patients with diabetes should be treated with low doses of metformin. In imaging procedures, metformin should be discontinued 2 days in advance. Metformin should be used in low doses or applied in an extended release form to reduce gastrointestinal side effects.

Sulphonylureas

They are powerful and fast-acting but have side effects, such as hypoglycemia and weight gain. Therefore, short effects, such as glipizide or slow release forms, should be preferred in the elderly. Due to the slow release forms, the risk of hypoglycemia is less than that of the old formulations. The risks of hypoglycemia are the age >75 years old, renal failure, heart failure, and dementia. The effects on heart failure and atherosclerotic cardiovascular disease are neutral. The effect on diabetic renal disease progression is neutral. In the ADVANCE study performed with the glylazide MR form, a decrease of 21% was observed on microalbuminuria.^[14] In the UKPDS study, microvascular risk reduction was demonstrated.^[16]

Non Sulfonylusion Secretegog Glinides

The effect starts quickly and ends fast. It is more expressed on postprandial blood glucose. These properties are preferred in postprandial hyperglycemia. Its use is very limited, and its combination with other drugs is inevitable. Particularly preferred is the combination with metformin and/

or basal insulin, which has effect on fasting blood glucose. However, hypoglycemia and weight gain are the most undesirable for the elderly. In addition, taking the drug before each main meal is an advantage in terms of flexible use in those who have a habit of eating irregularly, but the need to use it three times a day is a disadvantage that reduces drug compliance. The effects on heart failure, atherosclerotic heart disease, and diabetic nephropathy are neutral. Because 90% of the repaglinide is excreted with bile, it can be easily used in renal failure. Nateglinide is contraindicated in renal insufficiency because of the 80% renal excretion. Glinides may not be effective in patients with prolonged diabetes, such as sulphonylureas.^[17, 18]

Glitazones

Glitazones, which are nuclear receptors and PPAR agonists, are the lowest antidiabetic agents with a hypoglycemic effect. Large randomized prospective cardiovascular outcome studies have shown strong evidence that pioglitazone may delay the atherosclerotic process (PERISCOPE and CHICAGO studies)^[19, 20] and reduce cardiovascular events (IRIS and PROactive studies),^[21, 22] but its use is limited in the elderly. The most important reasons for this are edema, heart failure risk, increased fracture risk, and weight gain. Initial concerns about the increase of bladder cancer have decreased. In spite of these, it can be used with low doses in the early elderly group because of its benefits in secondary prevention of macrovascular diseases, such as myocardial infraction (MI) or stroke.^[23–26]

DPP-IV Inhibitors

DPP-IV inhibitors reduce HbA1c by 0.6%–1%. The DPP-4 inhibitor can be preferred in the elderly because of the low side effect of hypoglycemia and no weight gain. Also, it can be preferred in the elderly who have the habit of eating irregularly, that is, who neglect or forget to eat. It has been shown that the risk of heart failure increases with saxagliptin and alogliptin.^[27] The dose should be adjusted in the renal failure except for linagliptin. If GFR >50 ml/min, it should be continued with 100 mg sitagliptin, 50 mg sitagliptin for GFR 30–50 ml/min, 25 mg sitagliptin for GFR <30 ml/min, and in hemodialysis/peritoneal dialysis (because it is excreted unchanged in the urine). Saxagliptin 2.5 mg is used safely and effectively in moderate-to-severe renal failure. Vildagliptin at a dose of 50 mg can be used in moderate and severe renal failure, without the need for dose change in mild CRF.

GLP-1 R Agonists

The GLP-1 R agonists reduce HbA1c by 1.0%–2%. The weight loss effect and low hypoglycemic side effects are

both advantages and disadvantages for the elderly. The effect on heart failure is neutral. As shown in the LEADER study, there was a decrease in nonfatal MI or nonfatal stroke in the presence of cardiovascular disease with liraglutide.^[28] Also, in semaglutide and in type 2 diabetes, cardiovascular death was shown to decrease in nonfatal MI or nonfatal stroke.^[29] Liraglutide has also been shown to have positive effects on the progression of diabetic renal disease. It has been reported to be effective and tolerable in the study performed with weekly exenatide in the elderly.^[30] Despite all these positive effects, it should be used with caution in the elderly due to its weight-loss effect and gastrointestinal side effects.^[31]

SGLT2 Inhibitors

SGLT2 inhibitors reduce HbA1c by 0.5%–1.0 %. It is a suitable option in the elderly because of low hypoglycemic side effects, the weight-loss effect, and beneficial effects in heart failure, but the risk of genitourinary infection, dehydration, and fracture should not be ignored. Beneficial effects of canagliflozin and empagliflozin on heart failure, atherosclerotic cardiovascular disease, and diabetic renal disease progression were demonstrated, but the risk of amputation at the foot metatarsal and foot fingers was found to be high with canagliflozin.^[32–34] In patients with diabetes over 65 and over 75 years of age, the efficacy of dapagliflozin in the treatment lasting for 2 years was found to be higher than in the younger group.^[35] Because there is a GLP-1 receptor in the glomeruli, a diuretic effect can occur, so attention must be paid to the use of ACEI. SGLT2 inhibitors and furosemide diuretics should be used with caution because of an increase in creatinin. The risk of fracture increase was shown in canagliflozin, but not in empagliflozin and dapagliflozin (Table 5).

Table 5. Risk of fracture in SGLT2 inhibitors	
Risk of fracture and SGLT2 inhibitors	
Canagliflozin	Empagliflozin and Dapagliflozin
<ul style="list-style-type: none"> • Decrease in BMD • Increase in fracture (4% vs. 2.6%). In those with a history of CV, in those with low GFR, the risk of high-dose diuretics increases (CANVAS study) • Meta-analysis showed no significant increase in the fracture risk (OR 1.15, 95% CI 0.71–1.88) 	<ul style="list-style-type: none"> • Increased risk of fracture not shown

Insulin Treatment

When the first diagnosis of diabetes is made in the elderly, the diagnosis of Type 1 diabetes should be excluded. If the C-peptide level is found to be low in patients with low-diabetes, the C-peptide level is found to be low. If LADA or Type 1 diabetes is diagnosed, intensive insulin therapy should be performed. The most important point in the treatment of insulin in elderly diabetics is to give the patient the ability to monitor insulin. In patients who use insulin, not only HbA1c monitoring, but also the patient’s own glucose monitoring should be considered.

Patients with diabetes and hypoglycemia education should be given importance. Excessive insulin dose should be avoided by follow-up. Overdose insulin is not desirable because of both hypoglycemia and weight gain. Insulin treatment should be individualized, and the infrequent injection regimens should be used. In case of failure with OAD, basal insulin should be added to the current treatment and, if necessary, a basal + plus regimen should be planned by adding bolus insulin 1 or 2 or 3 times per day to meals. Again, premixed insulin regimen 1 or 2 or 3 times per day may be a good option.

Oral Antidiabetic Drug use in Elderly Diabetics with Neurological Disease

The incidence of hypoglycemia is directly related to dementia. In addition, hypoglycemia is a triggering factor for Alzheimer’s disease by causing hippocampal atrophy. It has been suggested that sulfonylureas increase the risk of Parkinson’s disease, whereas metformin decreases it. Pioglitazone has been reported to be protective against to Parkinson’s disease.^[36–38]

Conclusion

Although the diabetes treatment approach does not differ in healthy elderly individuals, hypoglycemia is one of the most feared conditions, especially in the elderly. Therefore, metformin, DPP-IV inhibitors, and SGLT2 inhibitors should be considered first, with less risk of hypoglycemia. Low-dose sulfonylureas may also be used in selected cases. Insulin treatment should be individualized and the most rare injection regimens should be used. In case of failure with OAD, basal insulin should be added to the current treatment and, if necessary, a basal + plus regimen should be planned by adding bolus insulin 1 or 2 or 3 times per day to meals. The use of new antidiabetic drugs, such as GLP-1 analogues and SGLT2 inhibitors, has strengthened our ability to cope with the risk of hypoglycemia and cardiovascular events, which are the two most important drawbacks in the treatment of elderly people with diabetes. In elderly diabetics, inadequate treatment or excessive treatment and individualizing the treatment should be the most appropriate approach.

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