

Treatment of type 2 diabetes mellitus in the elderly – Special considerations

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ABSTRACT

Type 2 diabetes is a frequent chronic disease. Given its strong positive association with older age, it is a significant public health issue in elderly populations. Furthermore, the aging of the population, driven by increasing life expectancy in high and middle-income countries leads to an increasing prevalence of diabetes.

Although the same diagnostic criteria apply to the elderly and to younger people, there are unique aspects to the care for elderly type 2 diabetes patients. Both treatment goals and preferred medications, as well as non-pharmacological approaches should be adjusted in the elderly. For example, increasing the amount of physical activity may encounter difficulties, while introducing an appropriate diet may be more challenging. The patients' therapeutic adherence requires special attention due to cognitive and physical limitations. The most important treatment goal is to avoid hypoglycemia. Frailty, social and economic issues, comorbidities and the consequent polypharmacy frequently causing drug-drug interactions, as well

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as the increased danger of drug toxicity due to renal failure are only some of the problems that make the health care for old diabetes patients extremely difficult. Adequate care requires cooperation from a multidisciplinary team of health care professionals.

Acute diabetes complications have a higher mortality in the elderly, thus close attention must be paid to avoid them. Family members should be involved in the care of elderly diabetes patients, and it is recommended to educate them on clinical signs of complications. Regular care for the patients including feedback on quality of life and early signs of health issues are essential.

KEYWORDS

elderly, aging, geriatric patient, type 2 diabetes mellitus, anti-diabetic treatment

INTRODUCTION

The overall prevalence of diabetes mellitus (DM) is increasing worldwide. While it is estimated that 10.5 percent of the U.S. population has diabetes, only 8.2 percent have been diagnosed with the disease [1]. Based on epidemiological data from 91 countries it is estimated that the number of diabetes cases will increase by 54% between 2010 and 2030 [2].

Most patients diagnosed with diabetes (approximately 90%) have type 2 diabetes (T2DM). The prevalence of T2DM increases with the age until about 70 years of age with some decrease in the oldest old probably due to healthy survival bias [3]. As a consequence of continuously increasing life expectancy in the last decades, the proportion of elderly people is becoming higher and higher in high-income countries [4]. Consequently, we expect a steadily growing number of T2DM patients worldwide [5]. Diabetes is associated with several chronic complications, including microvascular disease (such as retinopathy, nephropathy, and neuropathy), and macrovascular disease (such as coronary heart disease, stroke, and peripheral arterial disease). Vascular disease in diabetes is the leading cause of vision loss and blindness as well as chronic kidney disease and end-stage renal disease in the United States [6, 7]. In addition to life-threatening conditions, diabetes complications are associated with decreased quality of life and may contribute to the loss of independence of elderly patients [8]. Neurocognitive dysfunction (including mild cognitive decline and dementia) is also more frequent in elderly people with diabetes compared to their non-diabetic peers [9, 10]. Given that diabetes develops at younger ages due to the obesity epidemic and people living longer lives, the duration of diabetes is getting longer in general that promotes the development of chronic complications [11].

Among the acute complications of diabetes, severe hypoglycemia, lactate acidosis, hyperglycemic hyperosmolar coma, and ketoacidosis are the most dangerous. Hypoglycemic events pose a diagnostic problem in the elderly because other conditions (such as stroke) that are more frequent in the elderly can present with similar symptoms [12]. Age-related comorbidities, such as congestive heart failure and chronic kidney disease increase the risk of lactate acidosis, highlighting the importance of rigorous monitoring and medication adjustments.

Treatment goals and preferred drug strategies are different in aged diabetic patients compared to younger ones. Our primary concerns should include (1) patient safety, (2) avoidance of acute complications and (3) optimized quality of life.



To reach these goals, a closely cooperating multidisciplinary team is required. Education of the patient, their family members, and caregivers on proper home care including lifestyle treatment (medical nutritional therapy and physical activity) and therapeutic adherence may be more challenging than the same for younger patients.

EPIDEMIOLOGY OF T2DM IN THE ELDERLY

Diabetes is the fifth leading cause of death worldwide that resulted in 1.6 million deaths [13, 14]. Diabetes was estimated to contribute to 11.3% of deaths globally in 2019 [15]. The prevalence of T2DM has been continuously growing in the past decades and this trend is expected to continue. This is driven partly by the aging of the population (the relative frequency of the elderly is increasing within the population), partly by the westernized lifestyle of people (leading to the obesity epidemic). Given the very high prevalence of T2DM in the elderly (reaching 25–30% in those 70 years of age), one should expect a massive number of old patients with diabetes by 2030 [16, 17].

For example, the prevalence of T2DM among U.S. adults aged ≥ 65 years is around 25% [1, 18]. Furthermore, T2DM is considerably underdiagnosed: more than 2 million older adults in the USA may have undiagnosed diabetes mellitus [1]. This high prevalence affects both men and women as well as populations with different racial and ethnic backgrounds [19]. As far as European countries are concerned, there is a slightly lower prevalence in those above 65 years of age (approximately 20%, ranging 14–30%) [20].

The descriptive epidemiological data are strongly influenced by the method used for diagnosis. Furthermore, the overlap between hemoglobin A1C-(HbA1c) based and oral glucose tolerance (OGTT) based diagnostic is limited [21, 22]. One-third of patients diagnosed by an OGTT were not diagnosed by HbA1c. Furthermore, even during an extended follow-up, only 60% of OGTT-diagnosed cases were confirmed by a diagnostic HbA1c [23].

PATHOPHYSIOLOGY OF DIABETES IN THE ELDERLY

T2DM is determined by genetic and environmental factors. Family history of T2DM is associated with an increased risk of T2DM as well as an earlier age at onset of the disease. In elderly populations, the role of genetic factors is getting smaller, while environmental factors and age-related changes in carbohydrate metabolism are becoming more important. Alterations in glucose-induced insulin release and resistance to insulin-mediated glucose disposal are both parts of these changes.

T2DM develops if both essential factors of normal glucose homeostasis become inadequate: insulin secretion from the pancreatic beta-cells gets insufficient for the glucose sensitivity of the peripheral cells [24]. In the elderly, both components are impaired [25]. According to epidemiological data, insulin resistance is a distal risk factor for diabetes development that is present at least a decade before diabetes diagnosis, whereas beta-cell insufficiency can be proven only 2–3 years before diagnosis [26].

Some important factors contributing to insulin resistance are central obesity, physical inactivity, subclinical inflammation, vitamin D deficiency, and hypomagnesemia [27]. The beta-cell



response to incretin hormones and also the pulsatility of hormone secretion becomes impaired in the elderly, proving that alterations in glucose-induced insulin release are essential components of aging-related changes in carbohydrate metabolism [28, 29]. Lifestyle interventions aiming at 150 min of moderate intensity physical activity and 5–8% weight loss were found to decrease the risk of T2DM development by 58% in middle-aged people with prediabetes [24]. Other dietary factors may also have an impact on the risk of T2DM in the elderly. An unhealthy dietary pattern (for example, high in saturated fats and simple sugars and low in complex carbohydrates) is associated with an increased risk of T2DM [30]. The lifestyle of elderly people is strongly affected by the presence of comorbidities. Furthermore, multiple drugs, the presence of obesity could also impair insulin sensitivity in the elderly. Free radical production in elderly diabetic patients is significant, and administering the antioxidants vitamins C and E can improve insulin action and metabolic control. Supplementing zinc and magnesium can also improve glucose metabolism in these patients [31].

The presence of low-grade inflammation in the normal aging process is well documented [32, 33]. Elevated levels of C-reactive protein and pro-inflammatory cytokines (such as interleukin-1 (IL-1) and tumor-necrosis alpha) as well as decreasing levels of anti-inflammatory cytokines (such as adiponectin and IL-1 receptor antagonist) may also contribute to the development of T2DM in the elderly [34–37]. Sex hormones, mainly sex hormone-binding globulin and testosterone are also involved in the development of diabetes in people of advanced age [38, 39].

Non-insulin-mediated glucose uptake (NIMGU), or so-called glucose effectiveness plays a significant role in postprandial glucose uptake (mainly in the brain). This means that glucose can stimulate its uptake in the absence of insulin. Older people have impaired glucose effectiveness and this impairment is more pronounced in people with diabetes [40].

Autoimmune phenomena can also be found in the elderly. A special subgroup of type 1 DM is LADA (late autoimmune diabetes in adults) that is characterized by beta-cell failure and high titers of anti-islet and anti-GAD (glutamic acid decarboxylase) antibodies. LADA leads to the profound impairment of glucose-induced insulin secretion and could sometimes be found in nonobese older patients incorrectly treated as T2DM [41].

Another important difference of the physiology of carbohydrate metabolism between older and younger patients is the more pronounced impairment of the counter-regulatory system. A lower cutoff for the initiation and a reduced response of glucagon and growth hormone to hypoglycemia are found in elderly subjects with diabetes [42]. This also means that the inadequate secretion of glucagon lowers postprandial hepatic glucose production, leading to hypoglycemia. Incretin hormones augment the counter-regulatory response, particularly glucagon secretion, thus defending against hypoglycemia [43].

SCREENING FOR DIABETES IN THE ELDERLY

The treatment of screen-detected prediabetes could prevent or delay the development of type 2 diabetes and there is some evidence that this could also lead to a decreased risk of vascular complications. For screen-detected diabetes the evidence is even weaker for the association of early treatment of diabetes and vascular complications [24, 44]. However, given the high frequency of T2DM and vascular diseases and their consequences (such as increased mortality,



frequent hospitalization, frequent emergencies, and frequent cardiovascular complications) in the aged population, screening of T2DM is generally accepted in the literature [45].

The same diagnostic criteria apply to the elderly as to younger patients. A random plasma glucose concentration $\geq 11.1 \text{ mmol L}^{-1}$ with typical symptoms of diabetes (like polyuria, polydipsia, and unexplained weight loss for type 1 diabetes) or a fasting plasma glucose concentration $\geq 7.0 \text{ mmol L}^{-1}$. For those with an elevated pretest probability of diabetes (for example a fasting plasma glucose (FPG) level between 6.1 and 7.0 mmol L^{-1}), a 75 g oral glucose tolerance test (OGTT) is advised. If two hours after the ingestion of a glucose solution the plasma glucose concentration is $\geq 11.1 \text{ mmol L}^{-1}$, diabetes can be diagnosed. In the absence of clinical symptoms, an elevated diagnostic blood sugar level requires confirmation [46].

HbA1c is also a valuable marker for the diagnosis of diabetes mellitus. An HbA1c $\geq 48 \text{ mmol mol}^{-1}$ (6.5%) value is diagnostic of diabetes [47]. HbA1c has several advantages over a glucose-based diagnostic test including lower within-person variability, no requirement for fasting, and a less labour-intensive determination. Furthermore, it was found in the population-based Whitehall II study that people whose OGTT-based diagnosis did not meet HbA1c criteria for diabetes during follow-up had a similar long-term cardiovascular disease risk as the background population, suggesting that the current change from the OGTT-based to HbA1c-based diagnostic approach is not harming people, but rather appears beneficial [23]. Determination of HbA1c has several limitations that should be taken into account in the elderly: conditions with shortened red blood cell lifespan (such as anemia and acute illnesses) could bias HbA1c readings and thus diabetes diagnosis [48].

Different diagnostic tests identify different people and have associations with different aspects of the pathophysiology of T2DM. For example, elevated FPG values are mostly determined by endogenous glucose production and reflect hepatic insulin resistance. Postload glucose values represent early- and late-phase insulin secretion and are better markers of peripheral insulin resistance and beta-cell dysfunction. HbA1c is a good reflection of overall glycemic status but not a good marker of prediabetic abnormalities and may be influenced by many factors unrelated to diabetes. [49, 50].

Prediabetes is an umbrella word that covers impaired glucose tolerance, impaired fasting glucose, and an HbA1c level of 39–47 mmol mol^{-1} (5.7–6.4%). The recognition of prediabetes is important as its treatment provides an opportunity to delay or prevent the progression to T2DM [24, 51].

The diagnosis of T2DM is easily missed in the elderly as its symptoms (such as fatigue, weight loss, polyuria, and blurred vision) can be attributed to other age-related conditions. The diagnosis is usually made as part of blood draws for unrelated symptoms or vascular screening. Given the lack of symptoms, regular screening of the elderly for diabetes is strongly recommended [25]. The importance of screening is further highlighted by the fact that T2DM is strongly associated with cardiovascular complications [52], brain atrophy, and dementia in the elderly [18, 53].

CLINICAL PICTURE OF DIABETES IN THE ELDERLY

In the elderly, most diabetes cases are T2DM. T2DM usually develops slowly and is generally symptomless or presents with few symptoms that are only indirectly related to hyperglycemia.



The diagnosis is further hindered by the fact that the elderly may have several clinical conditions that can mimic the symptoms of T2DM. Common aging conditions such as frailty, incontinence, and cognitive impairment make diagnosing even harder [54].

A typical symptom of diabetes is polydipsia. Polydipsia is caused by polyuria related to hyperglycemia and the thirst caused by fluid loss. With advancing age, the renal glucose threshold increases (due to chronic kidney disease), thus polyuria is not so pronounced as in younger diabetic patients. Furthermore, the feeling of thirst is decreased in the elderly, even in the presence of diabetes. Polyuria (if present) with decreased fluid intake is associated with the danger of dehydration as well as more severe hyperglycemia, potentially leading to an emergency.

Some geriatric syndromes may be further exacerbated by diabetes, such as sarcopenia, malnutrition, frailty, immobility, gait disturbance, incontinence, falls, functional decline, and delirium. The effect of diabetes on these syndromes seems to be bidirectional [25]. Regular screening of the elderly for geriatric syndromes is of utmost importance: not only for setting up a therapeutic plan for their treatment but also for taking into account their possible effects on diabetes care [55].

Depression is also more frequent in diabetes compared to non-diabetic individuals, and this is also the case in the elderly [56, 57]. Diabetes and depression share several symptoms, such as sleep disturbances, appetite and weight changes, and fatigue. In older adults, typical symptoms of depression (like depressed or sad mood) may be less evident, and anhedonia may be a better indicator of depression in the elderly. Depressed mood is often deemed to be a natural feature of aging, thus diagnosis is not always easy and may be delayed [58]. The care for people with diabetes associated with depression is hindered by the individual's ability to manage their diabetes successfully [59]. A combination of diabetes and depression is also associated with incident dementia and the development of complications, such as myocardial infarction, amputation, or loss of vision [60]. These complications, in turn, may worsen depression [56].

ACUTE DIABETES COMPLICATIONS IN THE ELDERLY

Hypoglycemia

The most feared acute complication of diabetes is hypoglycemia. It is one of the most common nonfatal complications in older patients with diabetes [61].

Hypoglycemia cannot be defined by one specific glucose level. The glycemic threshold for hypoglycemia is higher in those with poor glycemic control and infrequent hypoglycemic episodes. In contrast, it is lower in those with reasonable glycemic control or more frequent hypoglycemic episodes [62]. The reason for the lower threshold in those with frequent hypoglycemia is the combination of a defective counter-regulation with hypoglycemia unawareness, a status called hypoglycemia-associated autonomic failure. The American Diabetes Association (ADA) defined *iatrogenic hypoglycemia* as 'all episodes of an abnormally low plasma glucose that expose the individual to potential harm' [63]. More recent recommendations established three alert levels of low blood glucose concentrations: level 1, ≤ 3.9 mmol L⁻¹ (hypoglycemia alert); level 2, < 3.0 mmol L⁻¹ (clinically significant hypoglycemia); and level 3, severe hypoglycemia, associated with severe cognitive impairment requiring external assistance for recovery [64].



Hypoglycemia could lead to serious consequences, including acute and long-term cognitive changes, cardiac problems such as malignant arrhythmias or myocardial infarction, serious falls, long term frailty, or even death. Furthermore, hypoglycemic events could lead to hospitalizations, implying a substantial economic burden.

Clinical symptoms of hypoglycemia include excessive hunger, anxiety, tremor, sweating, cognitive impairment, confusion, and unconsciousness. In the elderly, the glucose range in which hypoglycemia is causing symptoms but does not yet lead to cognitive disturbances is narrower than in younger patients. This means that elderly patients have a shorter time window to treat the event. Furthermore, even if the patient is still aware of what should be done, he or she may no longer be able to perform it on his or her own. Given that a large proportion of the elderly live alone and nobody can give a helping hand, there is an increased hazard of loss of consciousness. Often the signs of hypoglycemia are mistaken for neurological symptoms or dementia, further delaying the recognition of hypoglycemia [65].

Patients, their family members, and their caregivers should be educated on the recognition of clinical symptoms and non-specific signs of hypoglycemia and on the actions required to treat the event.

Determining the risk of hypoglycemia and its potential consequences is extremely important before creating an individually tailored treatment plan. Risk could be enhanced in the elderly by common polypharmacy, low water intake, decreased intestinal absorption, changes in the pharmacokinetics and pharmacodynamics, and the common occurrence of cardiovascular and renal problems [66]. It is important to choose drugs with the lowest risk of hypoglycemia [67].

Hyperosmolar hyperglycemic state (HHS)

HHS is a medical emergency that has a high risk of death or disability. In general, it is associated with a substantially higher mortality than diabetic ketoacidosis (DKA) [68]. This syndrome is characterized by severe hyperglycemia, hyperosmolarity, and dehydration without acidosis. Plasma glucose levels can be extremely high, even around 100 mmol L^{-1} .

Comorbidities, the decreased feeling of thirst in the elderly, renal insufficiency, more relaxed glycemic control, nutritional errors, and intercurrent infections all are associated with increased risk of HHS. Common mechanisms underlying this clinical syndrome include dehydration, relative lack of insulin, and dysregulation of counter-regulatory hormones. HHS can occur without a known history of diabetes, as T2DM is frequently undiagnosed in the aged population. These patients are at higher risk for hyperglycemic crises due to dehydration than their younger counterparts [69]. Though treatment can result in full recovery, any delay in the diagnosis can lead to irreversible disabilities and conditions associated with a high mortality rate [70]. HHS is more frequent in geriatric patients than DKA, but DKA can occur with extremely high glucose values in the elderly that makes the situation even worse [71].

The most common precipitating factors for HHS are inadequate treatment (clinical inertia or patient non-compliance in 21–41%) and acute infections (in 32–60%) [72].

There is a prominent role of concomitant medications in precipitating HHS or DKA. Beta-adrenergic blockers, calcium-channel blockers, corticosteroids, and thiazide diuretics are associated with insulin resistance or reduced insulin secretion and are commonly used in the elderly [72].



Rehydration, restoration of electrolyte balance, and insulin treatment are the cornerstones of HHS therapy [73].

Diabetic ketoacidosis (DKA)

DKA is another acute emergency associated with hyperglycemia. Beyond the elevated blood glucose level, another characteristic of DKA is acidosis with an elevated anion gap due to the accumulation of ketone bodies. The diagnosis is supported by the presence of the following conditions: elevated blood glucose ($>13.9 \text{ mmol L}^{-1}$), acidosis ($\text{pH} < 7.3$), a serum bicarbonate level of $<18 \text{ mEq/L}$, and the presence of ketones in the blood and urine.

The main clinical symptoms are excessive thirst and hunger, frequent urination, nausea and vomiting, stomach pain, weakness or fatigue, shortness of breath, slurred speech, impaired recognition, and confusion.

Important signs of DKA include Kussmaul breathing, fruity-scented (acetone) breath, and signs of dehydration (for example, decreased skin turgor). Because skin elasticity is physiologically reduced in older patients, skin turgor should be checked on the inner aspect of the thighs and on the skin overlying the sternum, where its elasticity is best preserved.

Clinical symptoms usually evolve slowly, gradually. Diagnosis is not always easy in older patients, as tiredness, sleepiness, lethargy, neurological symptoms such as vision and speech disturbances, and unconsciousness can be confused with other common geriatric problems. Self-monitoring of blood glucose levels as well as regular check-ups could facilitate early recognition of metabolic disturbances.

In terms of differential diagnosis, abdominal pain may have significance, as it is specific for DKA (much less frequent in HHS). Abdominal pain in DKA is caused by the delayed emptying of the stomach and paralytic ileus due to metabolic acidosis and electrolyte abnormalities.

The most likely precipitating factors include infections (of the lower respiratory and urinary tract), therapeutic non-adherence [74], and also stressful events such as a stroke, myocardial infarction, trauma, or substance misuse. In up to 25% of DKA, there is new-onset type 1 diabetes in the background [72].

Treatment of DKA should include therapy for the underlying condition as well as rehydration, insulin initiation to normalize blood glucose levels, control of the electrolyte imbalance, and (in extreme cases) correction of acidosis.

Lactic acidosis (LA)

LA is another metabolic acidosis with elevated anion gap caused by overproduction or decreased elimination of lactic acid. The diagnosis of LA has even worse prognosis than DKA or HHS with a high mortality rate mostly related to the underlying systemic disease disturbing lactate metabolism.

Lactic acid may be overproduced by ischemic tissues due to local tissue hypoxia and in certain systemic and congenital conditions, cancer, and ingestion of certain drugs or toxins [75].

The risk of LA is elevated in patients with congestive heart, liver and/or kidney failure, conditions that are common in the elderly. Metformin, the first line antidiabetic treatment could also increase the risk of LA. Heart failure, liver failure, or renal impairment constitute relative contraindications for metformin treatment, however if more than one of these conditions are present in a patient, the use of metformin requires extreme caution. Old patients with



musculoskeletal symptoms frequently take non-steroid anti-inflammatory drugs, which can acutely worsen kidney function. Similarly, sepsis and alcohol consumption also increase the risk of LA.

The diagnosis of LA is based on the presence of acidosis ($\text{pH} < 7.35$) and an increased serum lactate level ($>5\text{--}6 \text{ mmol L}^{-1}$). There is no specific therapy of LA, and it should include treatment of the underlying disease.

CHRONIC COMPLICATIONS OF DIABETES IN THE ELDERLY

Chronic complications of T2DM are mainly caused by hyperglycemia-induced cellular and molecular impairment of neural and vascular structure and function. The most important chronic complications include macroangiopathy (i.e., cardiovascular diseases, stroke, peripheral arterial disease (PAD), and heart failure) and microangiopathy (retinopathy, nephropathy, and neuropathy). Diabetic vascular disease can manifest as myocardial infarction, disabling stroke, symptomatic arterial occlusive disease of the lower extremities, and blindness. All these complications profoundly influence both the quality of life and the life expectancy of diabetic patients.

Diabetic foot is a complex syndrome that is pathogenetically related to both macro- and microvascular diseases. Half of lower extremity amputations in high-income countries occur in diabetic patients that translates to a 15-fold increased risk compared to non-diabetic persons. Up to 80% of diabetes-related amputations may be preventable through optimal glycemic and vascular management and education [76]. Diabetes patients with a lower extremity amputation have a 67% 5-year mortality. Sensory neuropathy and arterial occlusive disease may be asymptomatic in the early phase in people with limited ambulation. Therefore, regular screening for sensory neuropathy (i.e. pin prick test) and PAD (i.e. ankle-brachial index) are crucial. Distal symmetric polyneuropathy can have negative (loss of sensation) or positive (pain, dysesthesia) symptoms and contributes to the development of the diabetic foot. DPN can present as pressure ulcers on foot due to an improper shoe that may be unrecognized because of the loss of protective sensation. Professional pedicure and individually designed neuropathic footwear could help preventing the development of pressure ulcers [77].

The most frequent underlying cause of end-stage renal failure and renal replacement therapy in developed countries is diabetic nephropathy. Diabetes, macrovascular and kidney diseases form a vicious circle [78].

Optimal glycemic control from the diagnosis of diabetes can prevent or delay the development of chronic vascular complications and thus can improve quality of life and patients' independence. However, the prevention and treatment of chronic vascular complications is a complex task that also includes optimization of blood pressure, blood lipid control, the appropriate use of antiplatelet agents, smoking cessation, and the use of antidiabetic medications with proven cardiovascular benefits. The chronic complications of T2DM are comprehensively discussed elsewhere [79].

TREATMENT GOALS OF DIABETES CARE IN THE ELDERLY

Treatment goals for diabetes in the elderly include maintaining proper glycemic control, preventing and treating acute and chronic complications. Treating and controlling comorbidities is



also essential [80, 81]. Clinical management must balance optimal glycemic control with the risk of hypoglycemic events and improved quality of life [65].

Treatment goals and the approach to treatment of young and elderly T2DM patients can be different. An important difference regarding treatment goals is that rigorous glycemic control is frequently not required in the elderly. On the one hand, the main concern of elderly patients relates to quality of life (such as loss of consciousness, occurrence of falls, and acute emergencies) that is strongly related to the risk of hypoglycemia. Falls are prevalent in elderly diabetes patients with hypoglycemia and could lead to many serious, life-threatening complications such as head trauma, immobility, and the need for surgery in general anesthesia. Besides increasing the risk of falls, hypoglycemia also means danger to the functioning brain cells, could result in worsening dementia and cardiac function. Since many old patients are on anticoagulant treatment, the consequences of falls could be even more serious. On the other hand, if the life expectancy is shorter than the time required for the development of vascular complications, strict glycemic control will not prevent these diseases.

As the group of elderly diabetes patients is very heterogeneous with differences in cognitive function, cardiovascular conditions and other comorbidities, the presence/absence of polypharmacy, social circumstances, financial possibilities, degrees of sarcopenia, and total body fat mass, elderly diabetes patients need individually tailored care plans. This plan needs to be based on a comprehensive geriatric assessment. In most elderly patients, the generally recommended HbA1c target of <7% could be relaxed based on the above risk factors and side effects.

PHARMACOLOGICAL TREATMENT OF DIABETES IN THE ELDERLY

The most important principles when selecting the optimal treatment for an old person with diabetes are to follow the current guideline algorithm but to make an individualized plan based on the patient's wishes.

Metformin

The first drug of choice for elderly diabetic patients as is for younger individuals is the biguanide metformin. It can also be used in patients with prediabetes as it is proven to delay the onset of diabetes. It has a complex, though not fully understood mechanism of action. Its main effect is the suppression of hepatic glucose production, but it also enhances insulin action in the periphery (mostly skeletal muscles), thus helps glucose uptake of the cells [82].

Some advantages of metformin should be mentioned, for example that it does not increase the risk of hypoglycemia, and that it may lower appetite and is mostly weight-neutral.

However, metformin treatment may also be associated with side effects that may be more prevalent in elderly patients. As metformin is eliminated through the kidneys, acute or chronic renal failure could lead to toxic metformin levels. Congestive heart failure and liver failure are relative contraindications for metformin treatment due to the increased risk of lactic acidosis. Long-term metformin use increases the risk of vitamin B12 deficiency that can exacerbate diabetic neuropathies and present with symptoms of neuropathy [83] that can be challenging to recognize. Thus, it is recommended to screen for vitamin B12 deficiency in patients on metformin over a duration of 4 years. Metformin could cause gastrointestinal symptoms (such as flatulence and diarrhea) that frequently lead to treatment intolerance, as many elderly patients



struggle with fecal incontinence. It is important that metformin should be discontinued at least two days before imaging procedures requiring iodinated contrast material.

Sulfonylureas

Sulfonylureas represent a group of medications that are used for the treatment of T2DM for the longest time. The first generation of these drugs had a long duration of action and a high frequency of hypoglycemic events, and thus their use is not advised any more. Glibenclamide, gliclazide, glimepiride, and gliquidone are second-generation drugs frequently used due to their low price and effectiveness. Sulfonylureas act by forcing insulin secretion of pancreatic b-cells irrespective of blood glucose levels. Thus the main concern with sulfonylureas is the risk of hypoglycemia that can be long-lasting and recurrent. People on sulfonylurea treatment presenting with severe hypoglycemic event should be hospitalized. As most of these drugs are eliminated through the kidneys, their use is not recommended for patients with renal failure (except for gliquidone) [84].

Glucagon-like peptide 1 receptor agonists (GLP-1 RA)

Glucagon-like peptide 1 is a gut-derived incretin hormone released by the trigger of food consumption. Release of GLP-1 results in glucose-induced (postprandial) insulin secretion and suppression of glucagon secretion. GLP-1 also slows down gastric emptying and partly through central nervous system effects decreases appetite. Representatives of this class of drugs are dulaglutide, exenatide, semaglutide, and liraglutide. They may help patients with obesity to lose weight and increasing evidence supports their beneficial effects on the risk of cardiovascular and renal outcomes. They might have some beneficial effect on retinal neurodegeneration [85] and platelet activation that could underlie their beneficial vascular effects [86]. They are generally safe, without the danger of hypoglycemia. Once weekly or oral preparations are attractive medications for the treatment of T2DM in the elderly, although their (sometimes severe) gastrointestinal side effects and increased risk of malnutrition should be balanced before treatment initiation [87].

Dipeptidyl peptidase 4 inhibitors (DPP4i)

DPP4i are also medications acting on the incretin axis. DPP4 has a crucial role in enhancing the clearance of incretin hormones (including GLP-1). By a decreased clearance of the incretin hormones, DPP4is increase postprandial insulin secretion and suppress glucagon secretion. It should be noted that DPP4is can produce much lower levels of incretin hormones compared to GLP-1R. As and thus their effect on blood glucose is much smaller, on weight gain it is neutral, while their safety profile is generally favourable.

FDA-approved representatives of DPP4is are sitagliptin, saxagliptin, alogliptin, and linagliptin, while vildagliptin is authorized only in Europe [88]. The combination of metformin with DPP4i is an effective choice, as metformin is capable of stimulating GLP1 secretion [89]. The DPP-4 inhibitors may be preferred in the elderly due to the low risk of hypoglycemia and the lack of other major side effects. The dose of some DPP4is should be adjusted to renal function.

Sodium-glucose co-transporter-2 (SGLT2 inhibitors)

It is one of the newer classes of oral anti-diabetic medications. By interfering with the SGLT2 enzyme in the kidneys, SGLT2 inhibitors help decreasing glucose reabsorption in the kidneys.



Decreased glucose reabsorption causes an elevated glucose level in the urine (up to 120g day⁻¹) and an increased amount of urine because of the osmotic effect of urinary glucose. Significant benefits of SGLT-2 inhibitors include their potent nephroprotective properties, decreased risk of cardiovascular events and substantial effect on hospitalizations due to heart failure [90]. Three major representatives of the SGLT2 inhibitor class are canagliflozin, dapagliflozin, and empagliflozin. Though SGLT2 inhibitors can effectively decrease the plasma glucose level, their application for elderly patients may be inconvenient and requires individual assessment due to the frequent occurrence of urinary incontinence and the increased risk of dehydration. Important side effects of these drugs are urinary and genito-urinary tract infections that should be monitored regularly. Advantages of these drugs for elderly patients include their low risk of hypoglycemia and their benefits in heart failure and atherosclerotic cardiovascular disease [91].

Insulin

The major pathophysiological underpinnings of T2DM include insulin resistance and decreased insulin secretion. Anti-diabetic drugs act on both of these abnormalities; however, the longer diabetes exists, the higher the probability of developing beta-cell failure that cannot be overcome by noninsulin antidiabetic medications. In this situation, insulin should be given alone or in combination with non-insulin anti-diabetic drugs, such as metformin, SGLT2 inhibitors, DPP4is or GLP-1 RAs.

In elderly patients with T2DM, the simplification of complex insulin treatment regimens can significantly improve quality of life with the use of modern basal insulins and combinations of basal insulins with GLP-1 RAs and SGLT2is.

Patterns for insulin administration should be as simple as possible, in order to decrease the risk of hypoglycemia, and improve patient adherence. Once daily basal insulin can be used as a morning injection, basal insulin can be given twice daily without meal-related insulin. When intensified insulin treatment is required (meal-related short-acting and long-acting basal insulin), analogue insulins are preferred over human insulins and the dose of basal insulins is usually increased in exchange of a decrease of meal-related insulins. For patients with a limited life expectancy or severe functional limitations, more relaxed glycemic targets can be applied.

The exact dosing of insulins could be a problem for elderly patients due to altered mental status or visual disturbances. Insulin treatment (especially short acting insulins) could also increase the risk of hypoglycemia. In patients with decreased appetite or for those forgetting to eat, meal-related insulin should be given based on the amount of carbohydrate consumed after the given meal.

For elderly patients with type 1 diabetes, insulin treatment is lifesaving, and intensified insulin regimens are recommended. The use of diabetes technology (including smart insulin pens, continuous glucose monitoring and hybrid closed loop systems) could improve glycemic control and decrease the risk of hypoglycemia in elderly T1DM and insulin-treated T2DM patients.

ABSOLUTE INDICATIONS OF INSULIN TREATMENT

- Type 1 diabetes mellitus
- Newly diagnosed symptomatic disease with severe hyperglycemia



- Poor glucose control despite aggressive oral therapy
- Intercurrent illness or surgery
- Renal disease
- Hepatic disease
- Allergy to oral medications
- Inability to tolerate oral medications

Non-pharmacological therapy in the elderly

Physical activity. Physical activity can effectively lower plasma glucose levels without the need for insulin action. Unfortunately, regular exercise may be challenging for the elderly because of frequent musculoskeletal problems and diseases of the central nervous system, such as Parkinson's disease. Older people dislike changing their habits, so it can be difficult to achieve a significant change of a sedentary lifestyle. It is important to educate the patient about the importance of physical activity and to find the least disturbing way to increase physical activity. Involving family members or caregivers may also be helpful.

There is a bidirectional relationship between the risk of sarcopenia and that of T2DM. Insulin resistance in skeletal muscle amplifies sarcopenia, while sarcopenia may hamper physical activity further decreasing insulin sensitivity. Increased physical activity has several benefits in the elderly such as the increase of muscle volume and strength, and it also improves glycemic control in diabetes. A combined exercise regime (including aerobic and resistance training) is recommended that should be adapted to the patient's performance status [92].

Medical nutrition therapy. Irrespective of the treatment choice, adequate nutrition remains the cornerstone of diabetes therapy. Calorie intake should be optimized based on the age, weight, height, level of physical activity, general health status. As weight loss related malnutrition can contribute to sarcopenia [93] and cognitive decline [94], the modern concept of nutrition therapy for the elderly targets not only glycemic control but also the prevention of sarcopenia, frailty, and dementia [95].

There are some particular issues concerning the proper diet of elderly diabetes patients [96]. Due to the diminished taste and smell in older adults can lead to decreased appetite. At the same time, a drop in the intensity of metabolism and physical activity leads to lower nutritional requirements as compared to younger persons. Depression may also be associated with a loss of appetite. Defective dentition is a frequent problem that influences the consistency and type of food the patient can eat.

There are some simple rules for a diabetic diet, which are especially important for the elderly. These are portion control, having regularly set mealtimes, limiting sugar, and eating fibrous, varied foods. Patients who are not able to control their diet may need the surveillance of their caregivers or family members. Regular meals are essential for patients who take anti-diabetic drugs with an increased risk of hypoglycemia (such as sulfonylureas and insulin preparations), as skipping a meal carries the risk of hypoglycemia.

In addition to the amount of carbohydrates, the quality of carbohydrates is also an important factor to be considered. Refined carbohydrates from foods like sweets, soft drinks, and desserts (with high glycemic indices) should be avoided, and complex carbohydrates with low glycemic indices, such as legumes, non-starchy vegetables, and fruits with high fiber content are preferred.



Complex carbohydrates are digested slower and are associated with lower postprandial peaks. The preferential source of protein intake should consist of lean meat and fish. Fats have the highest energy density among macronutrients, and most recommendations suggest limiting their intake if a reduction of body weight is required; however, any meal plan with a reduced energy content is equally effective in weight reduction. Among different fats, the intake of monounsaturated fatty acids is preferred. Eating whole grain cereals, nonfat or low-fat dairy products, as well as salt restriction are advised due to their cardiovascular benefits. Current guidelines have no strict advice on the ratio of carbohydrates and fat in total energy intake, and meal patterns (i.e., the Mediterranean diet) with proven vascular benefits are advised that take into account patient preferences.

A vital element of a healthy diet for the elderly would be high fiber content. Seniors with diabetes should consume more high-fiber foods, such as fruits, vegetables, and nuts, not only to prolong glucose absorption but also to control constipation, a frequent symptom in the elderly. A proper amount of fluid intake is also essential for the elderly. For diabetic patients, fluids with added sugar or fruit juices are discouraged. We have to emphasize the nice serving of food. Colorful dishes on a nice porcelain plate can increase appetite. We must also consider the patients' preferences and former dietary habits when creating dietary advice. The texture of the food should be adjusted to the health status and the swallowing and chewing ability of the patient. If the patient cannot eat it independently, the caregiver should be involved. Meals consumed together with family members or friends may also have a positive impact on appetite.

SOCIAL ASPECTS OF DIABETES CARE IN THE ELDERLY

Diabetes in the elderly is a rapidly increasing health problem, affecting postmodern societies. The hallmark of post-modernization is the accompanying lifestyle including dietary habits and consequential obesity, which are accurate predictors of T2DM. Some risk studies have confirmed the effect of traditional and novel predictors of diabetes. A Mendelian randomization study found 19 potential predictors and 15 protectors that influence the development of type 2 diabetes that include mostly long-known and some newly discovered elements [97].

Among the risk and protective factors, socio-demographic and socio-cultural elements were also identified, which act as behavioral, social situation-related, and cultural indicators. An important cluster of factors includes socio-cultural representations such as depression, smoking, coffee (caffeine) consumption, childhood and adult body mass index (BMI), body fat percentage, alcohol consumption, skipping breakfast, daytime sleep, short sleep duration, with later sleep disorder emerged as a new risk factor [97].

The social distribution of lifestyle and socio-cultural factors is sociological fact. The known dimensions of social inequalities (status factors) [98] influence the presence and effect of the above risk factors in the specific social groups both in the structural dimension and in the way of life (cultural dimension). The segmentation appears both in the class structure and in social stratification. In addition, they also form a social model insofar as they shape a society's cultural responses to post-modernization.

Based on the study of Clark et al., many external indicators influence and shape the background of diabetes development. These include the built environment, the level of education, the type of health care system, economic stability, and the social and community support system.



Based on their results, it is likely that individual social groups face the risk of diabetes unequally, primarily due to the differentiation of the chances of reaching the opportunities and endowments [99].

Other research and related publications show that ethnic and income differences, which are less external and more inherent social indicators, also influence the incidence of diabetes [100]. The authors highlight three important measures of socio-economic status: income, education, and occupation, and establish that all of them influence the development and the course of diabetes mellitus in a complex manner, just as in the case of other diseases. One of their main conclusions is that these factors impact the development of the disease either by themselves or in an interdependent manner. People at the bottom of the social hierarchy get sick and die earlier than people at higher levels. This social gradient extends to even populations higher on the hierarchy as supported by findings from the Whitehall II study. The study tries to justify the effect of housing problems and the related instability on diabetes with indirect causal explanations. The authors consider environmental food factors as predictors that can be associated not only with socio-economic status but also with socio-cultural factors: traditions, customs, values, etc. What is more, they create a “nutrition status” from all these factors, which affects the prevalence and incidence of diabetes in an integrated way. The issue of food safety is subject to a similar assessment.

Going beyond the pronounced socio-economic factors, authors of other research bring lifestyle-related social inequalities into the question of the frequency of the development of diabetes. Physical inactivity, household income, dietary habits, and obesity are the key factors that explain the prevalence of diabetes [101]. It is well established that the effect of socio-economic factors on the risk of diabetes development is mediated through well-known biological risk factors and lifestyle habits. Furthermore, the separation of lifestyle habits and risk factors of diabetes tracks from young age through adulthood.

Most research examining the social background of diabetes concludes that, similarly to other types of diseases, these indicators function as fundamental differentiating factors and divide the structure of society in terms of maintaining a healthy status and death.

CONCLUSION

In general, the diabetic population is getting older. Nowadays, approximately 48% of T2DM patients are over 65 years old, and this number is expected to increase. As clinical symptoms are scanty, screening using glycemic examinations are essential for the detection of diabetes. The same diagnostic criteria should be applied in younger and older people, and regular screening is advised. In people with limited life expectancy, the main therapeutic goal is to prevent acute complications, mainly hypoglycemia and consequent falls, and to prevent and to slow the worsening of sarcopenia, frailty, cognitive decline, and cardiac failure. The target glycemic range should be individually determined, and it is frequently not as low as in younger diabetic patients. The therapeutic plan should take into account the patient's body weight, comorbidities, life expectancy, social circumstances, and personal preferences. Treatment decisions should be based on the mutual agreement of the patient and the health care provider.



Nutrition and physical activity are the cornerstones of diabetes therapy that should complement pharmacological treatment. The involvement of family members and caregivers in the care of elderly diabetic patients is essential. Education and regular follow-up of patients and their helpers can contribute to lowering the risk of hospitalization of elderly diabetic patients.

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