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Cognitive dysfunction in patients with type 2 diabetes

Kognitivne motnje pri bolnikih s sladkorno boleznijo tipa 2

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Abstract

The prevalence of diabetes and dementia has been increasing in recent years. These two diseases share many risk factors, such as hypertension, dyslipidaemia, obesity, unhealthy diet, and physical inactivity. Poor glycaemic control is associated with a higher risk of cognitive decline, and both microvascular and macrovascular complications are related to a higher risk of dementia. Older people with diabetes experience deficits in several cognitive domains, especially memory and executive functions. Such problems can affect the course of the disease, individuals' ability to gain insight into their illness, and the ability to follow a treatment regimen. Cognitive dysfunction in diabetes patients relates to poorer diabetes knowledge and self-care, increased inaccuracies in blood glucose monitoring and insulin adjustment, frequently missed medical appointments, and a higher number of hypoglycaemic episodes and cardiovascular complications. It is important to identify cognitive dysfunction in diabetes patients and consider these problems in treatment planning, defining target glucose levels, planning education, choosing pharmacological and non-pharmacological methods, and providing supports to patients and their family members or caregivers. An individual approach, gradual changes, and a simple treatment regimen (e.g., use of extended-release drugs and pill dispensers) that consider the patient's social situation are of the utmost importance.

Izvleček

Prevalenci sladkorne bolezni in demence v zadnjih letih naraščata, bolezni pa si delita številne dejavnike tveganja, kot so hipertenzija, dislipidemija, čezmerna telesna teža, nezdrava prehrana in telesna neaktivnost. Pomanjkanje glikemičnega nadzora se povezuje z višjim tveganjem za kognitivni upad, mikrožilni in makrožilni zapleti sladkorne bolezni pa z višjim tveganjem za razvoj demence. Bolniki s sladkorno boleznijo imajo oškodovane različne kognitivne domene. Posebej izrazite so težave na področju spomina in izvršilnih funkcij. Tovrstne težave lahko vplivajo na potek sladkorne bolezni, posameznikove možnosti uvida v lastno bolezen in sposobnosti sledenja režimu zdravljenja. Kognitivne motnje pri bolnikih s sladkorno boleznijo se povezujejo s slabšim znanjem in slabšo skrbjo za lastno bolezen, pogostejšimi napakami pri

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spremljanju krvne glukoze in odmerjanju inzulinskih injekcij, pogosteje zamujenimi zdravstvenimi pregledi in večjim številom epizod hipoglikemije ter srčnožilnih zapletov. Pomembno je, da pri bolnikih s sladkorno boleznijo prepoznamo kognitivne težave in jih upoštevamo pri načrtovanju zdravljenja; opredelitvi tarčnih vrednosti, edukaciji, izbiri farmakoloških in nefarmakoloških načinov zdravljenja ter nudenju podpore bolnikom in njihovim svojcem oziroma skrbnikom. Pomembni so individualni pristop, postopno uvajanje sprememb in čim bolj enostaven protokol zdravljenja (npr. uporaba zdravil s podaljšanim učinkom, uporaba razdelilcev zdravil), ki upoštevajo tudi socialno situacijo posameznika.

1 Introduction

The global prevalence of diabetes was estimated at 171 million in 2000; this is expected to nearly double by 2030 (1). The increase in prevalence can be attributed to changing lifestyle factors such as unhealthy diet, obesity and physical inactivity, as well as longer life expectancy and population aging (2). The results suggest that the diabetes epidemic will continue even if the obesity prevalence remains unchanged (1). Patients with diabetes also have a higher risk of developing mild cognitive impairment (MCI) and dementia (3).

Dementia refers to a syndrome, usually chronic and progressive, characterized by a more pronounced cognitive decline than would be expected with normal aging (4). In dementia, dysfunctions of memory, thinking, orientation, comprehension, arithmetic, learning, speech, judgment, and functioning in daily activities are found. Alzheimer's dementia (AD) is the most common neurodegenerative dementia, followed by Lewy body dementia, mixed dementia, and vascular dementia. Mild cognitive impairment indicates cognitive changes in one or more domains without significant impact on daily functioning (5). Patients with MCI are at higher risk for cognitive decline and development of dementia. Population trends in diabetes are very similar to those in dementia: 5–7% of people over the age of 60 have dementia and the prevalence of dementia is expected to almost double every 20 years (6).

2 Risk factors

2.1 Dementia

Risk factors for the development of dementia can be classified into two groups. The first group includes modifiable risk factors; with prevention or reduction of their impact, we can reduce the risk of disease development or slow its progression. A recent meta-analysis (7) introduced 12 modifiable risk factors for dementia: low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, social isolation, excessive alcohol consumption, traumatic brain injury, and air pollution. Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which, theoretically, could be prevented or delayed. Although some risk factors are more pronounced in certain periods of life, e.g. education in early life, the authors stress that it is never too early and never too late for dementia prevention. The second group includes non-modifiable risk factors: age, female sex and the apolipoprotein (APOE) ε4 genotype, a genetic risk factor for Alzheimer's disease (8,9).

2.2 Diabetes mellitus

In recent years, metabolic syndrome, a set of clinical and metabolic factors, is frequently mentioned among the diabetes risk factors. Although the definitions for metabolic syndrome vary slightly, most include factors that are commonly concurrent: central obesity, impaired glucose tolerance, atherogenic dyslipidaemia, and arterial hypertension (10). The cause of the metabolic syndrome has not yet been completely explained. Insulin resistance plays an important role in the pathogenesis and is the cause of abnormal glucose and lipid metabolism, which can also affect the development of arterial hypertension. Metabolic syndrome is thus not only a risk factor for the development of diabetes but is also associated with a higher risk of cardiovascular disease and various types of cancer (11). A recent meta-analysis has shown that the association between metabolic syndrome and cognition in the elderly is quite inconsistent (12). The individual metabolic syndrome components show different patterns of association with cognition, as these associations are also influenced by age. A slightly older meta-analysis confirmed an association between metabolic syndrome and cognitive decline in younger (≤70 years), but not older (>70 years) elderly people (13). At the same time, metabolic syndrome is also associated with a higher risk of vascular dementia and higher risk of

progression from MCI to dementia (14). Early prevention and recognition of the metabolic syndrome is extremely important to reduce the risk of further complications.

2.3 Age-related risk factor characteristics

Obesity is one of the risk factors linking diabetes and dementia. Even though obesity is a generally accepted risk factor for dementia (7), the association between late-life obesity and dementia is somewhat more complex. In late life, a lower body mass index (BMI) is frequently associated with worse cognitive performance (15,16), however, with long-term follow-up, the detrimental effect of weight gain can be observed, a trend clearly observed in middle age. In old age, weight loss can be the result or a sign of developing dementia, which makes a higher BMI to appear protective with regard to cognitive function, an effect that is observed particularly in short-term follow-up (17). Similar patterns have been observed in cholesterol (18) and blood pressure (18); that the elderly with higher cholesterol levels and blood pressure exhibit better cognition. It is important to be aware of changes in the pattern of associations between certain risk factors and cognition in (late) age and to pay attention to this, particularly when rapid changes in certain areas occur, such as sudden weight loss.

Associations between risk factors, diabetes complications and cognitive impairment are shown in Figure 1.

3 Diabetes mellitus and cognition

Diabetes mellitus is an independent risk factor for poor cognitive function in the elderly (19), faster cognitive decline (20), and MCI (21). A systematic review of studies has shown that patients with diabetes have impairments in various cognitive domains with executive function and memory being particularly affected (22). Additionally, diabetes is also associated with cognitive decline in the global cognition, memory, executive function, and orientation over a follow-up period of 10 years (23). Some studies report that changes in the brain or cognitive problems can be detected in the pre-diabetic period (20), although the results in this area are not entirely consistent (19).

3.1 Hyperglycaemia and hypoglycaemia

Poor glycaemic control in diabetes, resulting in both hyperglycaemia and hypoglycaemia, is strongly associated with cognitive impairment (24). Variations in blood glucose levels that impact the brain can cause

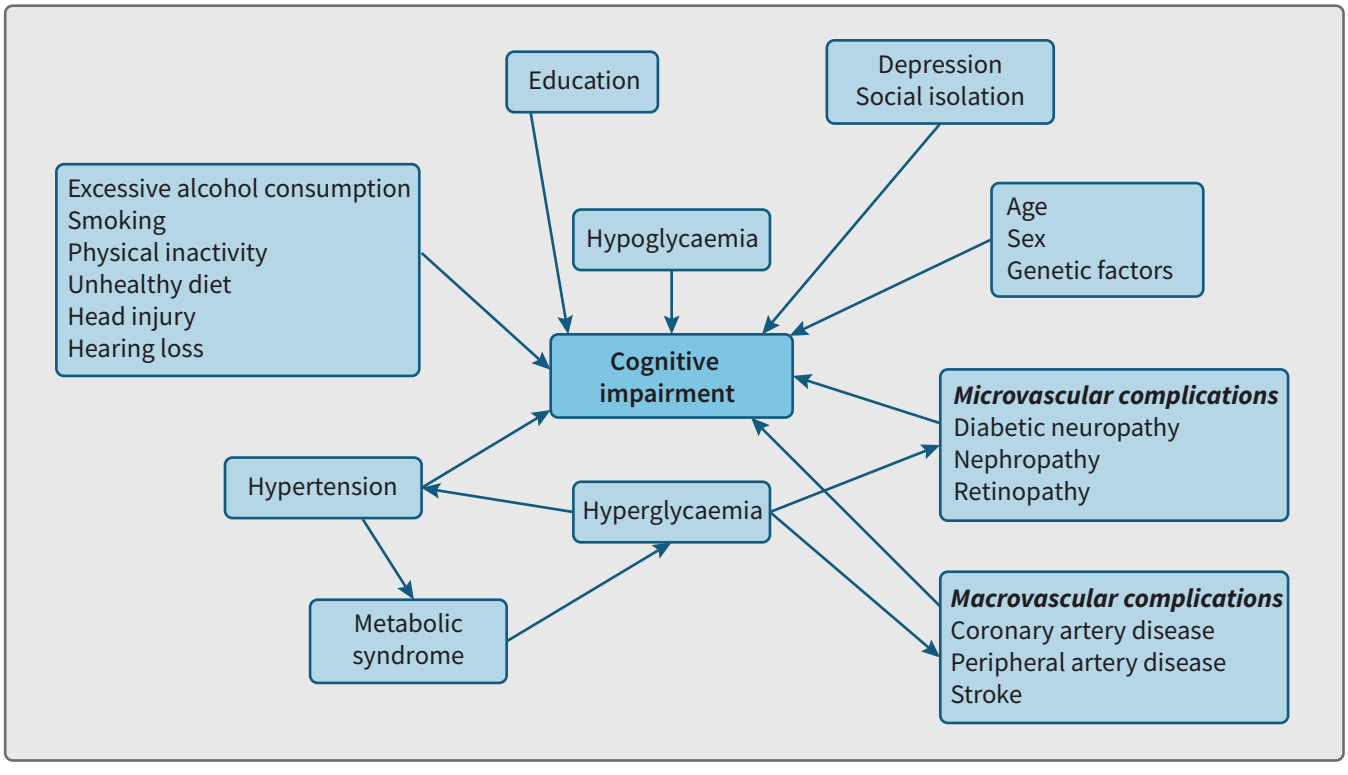

Figure 1: Associations between risk factors, diabetes complications and cognitive impairment.

a wide range of changes in brain function, from mild disorders to dementia or even death (25). Hypoglycaemia is the main reason for temporarily altered brain function in patients with diabetes (25). Cognitive impairment occurs because the brain does not have enough glucose to function normally. When the blood glucose level falls below 3.5 mmol/L, this can lead to various cognitive symptoms, such as confusion, unusual behaviour, impaired concentration or lack of focus, and poor coordination. As glucose levels rise, these symptoms usually disappear, but prolonged, recurrent hypoglycaemia may lead to cognitive decline. A history of severe hypoglycaemia is associated with a higher risk of cognitive decline and dementia (26), while recurrent hypoglycaemia also leads to poorer memory and slower processing speed (27).

At the same time, chronic hyperglycaemia is also associated with a higher risk of developing cognitive impairment (28). During an episode of acute hyperglycaemia, processing speed, working memory, and attention are impaired (29). In addition, patients are more dysphoric with reduced energetic arousal and increased sadness and anxiety. A study has shown that a composite index of hyperglycaemia can explain the changes in processing speed and executive function in diabetes (30). Hyperglycaemia is associated with two groups of typical diabetes complications that increase the risk of developing dementia (24). The first group includes microvascular complications, namely diabetic neuropathy, nephropathy, and retinopathy. The most common macrovascular complications include coronary artery disease, peripheral artery disease, and stroke (31). High glucose levels accelerate the process of atherosclerosis, leading to important micro- and macrovascular diseases affecting the heart and brain and cause changes in brain function (25). Epidemiological studies have shown that diabetes and related conditions are associated with both vascular and neurodegenerative forms of cognitive impairment, but the association between diabetes and vascular forms of cognitive impairment is stronger and more consistent (32).

3.2 Types of cognitive impairment in patients with diabetes

Different manifestations of cognitive problems can be observed in patients with diabetes. In their article, Koekkoek et al (33) presented three stages of diabetes-associated cognitive dysfunction. Individual stages do not necessarily represent a continuous process, but they can lead to different outcomes. The authors differentiate between diabetes-associated cognitive decrements, MCI, and dementia. For the latter two, the same diagnostic criteria as for patients without diabetes apply, but mild cognitive changes that appear in patients with diabetes are frequently missed. These minor changes occur in all age groups and progress very slowly with aging. Diabetes-associated cognitive decline is normally recognized after patients report changes in their cognitive function; normally, they report of increased mental effort without changes in their professional and social activities. At the same time, there is no alternative explanation for these complaints. Cognitive problems should not be so severe as to be classified as MCI. In fact, diabetes-associated cognitive decline corresponds to the clinical diagnosis of subjective cognitive complaint. Although symptoms may not be particularly severe, the diagnosis remains important as it acknowledges the patient's experiences; at the same time, subjective cognitive impairment frequently reflects preclinical Alzheimer's dementia (34).

In addition to assessing the severity of cognitive impairment, it is extremely important to identify which cognitive domains are impaired (35), as these affect the specific symptoms that patients have. Based on these symptoms, treatment can be tailored to the patient, offering adequate support. Patients with memory problems, for example, can forget to take medication or eat on time. Patients with executive function impairment normally have good working memory and remember instructions given to them but find it difficult to abandon old behaviours and routines and start new ones. Therefore, the patient's behaviour may be misinterpreted as inconsistent or stubborn. Individuals who have problems with mental flexibility and processing speed will have problems if treatment regimens become too complex. They may experience anxiety and fear of not being able to follow the treatment plan. Those who have trouble solving problems, however, may remember the instructions but are unable to integrate them into practice. They also experience problems with recognizing and treating hypoglycaemia.

3.3 Recognizing patients with cognitive impairment

The question arises as to whether patients with diabetes should also be routinely screened for possible cognitive impairment. In patients with diabetes over the age of 65, the American Diabetes Association

(36) recommends neuropsychological assessment at first visit and yearly assessments with tests such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) or Mini-Cog if so required. The European Diabetes Working Party for Older People (EDWPOP) recommendations (37) state that a yearly cognitive assessment should include the global/physical, cognitive and affective domains of functioning.

The authors of the previously presented three-stage model of diabetes-associated cognitive decline (33) propose a case-finding strategy, combined with appropriate support for diabetes management. Such case-finding strategies should focus on detection of MCI and dementia since these disorders are most likely to have implications for daily function and diabetes self-management. The focus should be on individuals who are more likely to develop cognitive impairment, such as patients with frequent hypoglycaemic episodes or patients who have started using new drugs because they have not achieved the desired efficacy with the previous ones. One of the possible approaches is assessing an individual's risk to develop dementia. An example of this is a short risk score for predicting the 10-year dementia risk, which was designed specifically for patients with type 2 diabetes (38). It includes an assessment of predictors most strongly associated with dementia, namely age, education, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event, and depression. In diagnosis, it is important to pay attention to depression as it may be associated with cognitive impairment. Possible explanations for cognitive complaints include hypothyroidism, vitamin deficiency, anaemia, liver disease, and kidney disease (33).

4 The effect of cognitive impairment on daily functioning and self-management

Diabetes self-management involves several cognitive abilities such as memory, attention, planning, and calculating, which is the reason cognitive impairment is associated with poorer self-management (39,40). Problems with memory and executive function are associated with poorer knowledge of diabetes, poorer insulin adjustment, increased inaccuracies in blood glucose monitoring, and more frequently missed medical appointments (22). At the same time, cognitive impairment is an important predictor of a larger frequency of hypoglycaemic episodes, cardiovascular complications, and deaths due to cardiovascular and other causes (41). With the help of focus groups, in their study, Feil et al (42) have studied what challenges caregivers face when caring for patients with diabetes and concurrent dementia. Three themes emerged. Memory loss caused patients to neglect self-care, leading to caregiver intervention. Behavioural and psychological symptoms of dementia disrupted the daily diabetes care routine, with denial of having diabetes being among the most common. Caregivers also reported that caring for both diabetes and dementia was highly burdensome as they felt overwhelmed and wanted more support from family and patients' healthcare providers. When planning treatment, it is important to pay attention to caregivers so that they also receive education about the disease and its treatment and receive appropriate support (43).

5 Treatment

5.1 Parameters of good diabetes management

Before we can focus on diabetes treatment strategies, it is important to identify appropriate glucose targets for a population of elderly patients with diabetes with associated cognitive impairment. The European Diabetes Working Party for Older People (EDWPOP) published guidelines on the treatment of patients ≥ 70 years with diabetes (37). It is recommended that treatment decisions be based on an assessment of the benefit-risk balance for each individual, taking into account factors such as hypoglycaemia risk, the ability to self-manage diabetes, the presence or absence of comorbidities, cognitive status, and life expectancy. The recommended haemoglobin A1c (HbA1c) values thus depend on age and comorbidities. A range of 7–7.5% is suggested for older patients with type 2 diabetes without major comorbidities and 7.6–8.5% for frail patients (including those with dementia) where the hypoglycaemia risk may be high and the likelihood of benefit relatively low. The article, which describes the consensus of experts in the field of diabetes treatment, states that health status, defined by the presence and number of comorbidities or impairments of functional status, leads to the identification of three major classes of older patients (44). For each of these classes, a specific glucose target value is recommended. A1c values <7.5 are recommended for healthy individuals or individuals with few comorbidities and intact cognitive and functional status. Those with a complex medical history should achieve A1c values <8.0. These are individuals with numerous chronic comorbidities but

only mild to moderate cognitive impairment. In individuals with very complex medical history and poor health, those who require long-term care, with end-stage chronic illnesses or moderate to severe cognitive impairment, A1c <8,5 is recommended. Recently, researchers have begun to emphasize that A1c should not be the only parameter used to define glycaemic targets in the elderly population. Studies have shown that A1c values in the elderly population do not necessarily reflect the same estimated average glucose values as in the younger population (35). Glucose self-monitoring is also recommended for a more realistic assessment of A1c in elderly patients with comorbidities.

5.2 Non-pharmacological treatment and support

Bunn et al (43) emphasize the importance of an individualized approach to treatment. In the early stages of dementia, when individuals still have enough functionality to make treatment decisions, both an individual approach and the formation of a relationship between the patient, their caregiver, and family physician are important. However, as dementia progresses and the patient's independent functioning becomes difficult, more attention should be paid to more accurate disease monitoring, both on the part of the caregiver and the family physician. The authors emphasize that emotional support and practical help provided by family members are crucial in this.

Munshi (35) gives a number of practical tips to help people with diabetes and associated cognitive impairment. In patients with memory loss (forgetting to take medications and insulin injections, monitoring glucose levels), it is recommended to use pill dispensers and send more than one appointment reminder. Patients should perform self-monitoring in the presence of caregivers or with their help. Long-acting formulations may reduce the frequency of administration as well as the number of insulin injections. In patients who have difficulty recognizing and treating hypoglycaemia and following new instructions, it is recommended that complex treatment regimens be avoided and that changes be made gradually. Patients may also benefit from repeating training and instructions at each visit. For individuals who have particularly severe difficulty in establishing new behaviours, we may ask caregivers for assistance when protocols are changed.

Patient education is also an extremely important area, which must be adapted in the case of cognitive impairment. German researchers compared the effectiveness of standard treatment and teaching programmes (TTP) to the structured treatment and teaching programme for elderly patients with type 2 diabetes mellitus and impaired cognitive function (DICOF-TTP) (45). This programme focused more on practical skills (e.g. injecting insulin) and repetition than on theoretical knowledge. Both groups of participants achieved the same results in the field of self-management after completing the training. However, at the follow-up examination six months later, those who attended the DICOF-TTP had better results and expressed higher satisfaction with the programme itself. The authors conclude that theoretical education alone is not sufficient to guarantee long-term learning in elderly patients.

5.3 Drug treatment

Poor glucose control in patients with type 2 diabetes is known to be associated with poorer cognitive function and faster cognitive decline (46). Human studies have shown that taking certain oral antidiabetic drugs can improve cognition in patients with MCI and dementia, but it remains unclear whether diabetes treatment can also reduce the incidence of MCI and Alzheimer's disease (Alagiakrishnan et al, 2013). Many antidiabetic drugs are thought to have a beneficial effect on neurogenesis and clinically improve cognitive and memory problems (47); they can also improve working memory (48).

There is still an open question as to whether a strict (intensive) pharmacological treatment regimen is better than a standard treatment regimen. Some studies report certain positive effects of intensive treatment on cognition (49), while other authors have found no evidence that different treatments affect cognitive impairment at all (50). Additionally, a more intensive treatment regimen is also associated with a higher number of hypoglycaemic episodes and higher mortality (49,50).

Each case should be evaluated individually to assess the benefits of a strict glycaemic control against the observed risks. Since complications are more common in the elderly, strict glycaemic control may be safer and more recommendable for type 1 diabetes, and standard treatment is recommended for patients with type 2 diabetes (49).

5.4 Guidelines for the pharmacological treatment of hyperglycaemia in patients with diabetes mellitus (and associated cognitive impairment)

Drug treatment represents an additional step of non-pharmacological treatment. Subsequently, based on the Slovenian guidelines for the clinical treatment of type 2 diabetes (51), we summarize the recommendations for the treatment of hyperglycaemia in patients with diabetes (Table 1). Lifestyle changes should be the basis of treatment, but efforts to make these changes are not a reason to delay the start of pharmacological treatment. The hyperglycaemia treatment protocol should be as simple as possible to ensure regular taking of medications. Gradually introducing drugs according to the level of glycaemia (HbA1c) and the severity of the hyperglycaemia symptoms is recommended. Treatment is usually started with a low dose of metformin, which is gradually increased. Renal function should be monitored. Metformin is contraindicated if the glomerular filtration rate (GFR) is below 30 ml/min/1.73 m^2.

If symptoms of hyperglycaemia persist despite the use of metformin, treatment with a sulphonylurea or insulin is required. Both drugs increase the risk of hypoglycaemia, so treatment should be started with low doses, which are gradually increased until glycaemic control is achieved.

When the patient has no symptoms of hyperglycaemia, treatment that does not increase the risk of hypoglycaemia, such as dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium glucose transporter inhibitors 2 (SGLT2-1) or glucagon-like peptide-1 (GLP-1), is preferred. DPP-4 inhibitors are safe drugs because side effects are uncommon; at the same time, they are less effective in lowering glucose compared to sulphonylureas and metformin. A fixed combination with metformin is possible, with taking medication on time being important. SGLT2 inhibitors are very effective drugs as they lower glucose by acting on the pancreas. The most common side effect is urogenital infection, and the risk of hypovolaemia and dehydration is also increased. In patients taking SGLT2 inhibitors, good hydration and consistent genital hygiene are important, which can be difficult to achieve in patients with cognitive decline. GLP-1 analogues are safe drugs as they do not cause hypoglycaemia. Side effects are common, particularly at the start of treatment, but normally disappear within a few weeks. They are suitable for people with a BMI over 30. Weekly formulations are available, which is important if the burden of

Table 1: Guidelines for the selection of hyperglycaemic agents in the treatment of type 2 diabetes.

Drug	Efficacy	Hypoglycaemia risk	Warnings	Dosage regimen	Formulation
Metformin	++	-	Monitor GFR	Once daily	Tablet
Sulfonylurea	+++	+		One to two times a day	Tablet
Repaglinide	++	+		One to three times a day with meals	Tablet
DPP4 inhibitor	++	-		Once daily, in combination with metformin twice daily	Tablet
SGLT2 inhibitor	+++	-	Dehydration, urogenital infections	Once daily, in combination with metformin twice daily	Tablet
GLP-1 analogue	+++	-	Nausea, vomiting, constipation	Once daily to once weekly	Injection
Acarbose	+	-	Bloating, flatulence	One to three times a day with meals	Tablet
Insulin	+++	+		One to four times a day	Injection

Legend: DPP4 – dipeptidyl peptidase 4; SGLT2 – sodium glucose co-transporter 2; GLP-1 – glucagon-like peptide-1; GFR – glomerular filtration rate.

administering medication to a patient falls on relatives.

If patients express problems related to the ability to follow treatment, they can also be alleviated by adjusting the treatment protocol (35). In case patients frequently forget to take insulin with a meal, the use of basal insulin and non-insulin preparations to control postprandial hyperglycaemia is recommended. If patients make mistakes in insulin dosing, it may be more sensible to determine the doses in advance. If the use of the scheme cannot be avoided, it can be simplified somewhat. For example: for glucose> 15 mmol/L we prescribe the use of one unit and for glucose> 20 mmol / l the use of four units of insulin. If patients experience hypoglycaemia for several hours after a meal and have high glucose levels during the day, it is recommended to use basal insulin in the morning and dose titration to ensure glucose control until the next morning. A possible solution is also the previously mentioned combination of insulin with non-insulin preparations. In case patients need a caregiver to administer insulin, a treatment regimen with as few injections as possible should be chosen. Problems with taking medications on time can be alleviated by using pill dispensers and using long-acting formulations.

It is currently unclear whether the use of acetylcholinesterase inhibitors (drugs registered to treat Alzheimer's dementia) brings specific benefits to patients with diabetes, as this has not yet been evaluated specifically for this subgroup of patients.

6 MOPEAD Results

6.1 Study description

In the following, we present the Slovenian results of the European project MOPEAD (Models of Patient Engagement for Alzheimer's Disease) (52), aimed at introducing new approaches for the early detection of individuals with signs of Alzheimer's disease. By comparing new approaches, we wanted to discover better ways to identify and diagnose this disease. We focused on individuals whose problems in the community are frequently overlooked, comparing four different strategies: a) online neuropsychological testing b) neuropsychological testing at the Department of Neurology at the University Medical Centre Ljubljana with an "open house" strategy c) testing in individual family medicine clinics and d) testing in specialist tertiary diabetes clinics. In individuals from specialist diabetes clinics, the criteria for inclusion in the study were a score of ≤ 27 on the MMSE and ≥ 7 points on the diabetes specific dementia risk score (DSDRS), which included several clinical and demographic variables, namely age, sex, education, diabetic foot, acute metabolic events, depression, microvascular disease, cardiovascular disease, and cerebrovascular disease. In study participants, a full diagnostic evaluation was performed, which included a neurological and physical examination, neuropsychological assessment, assessment of functional status, assessment of resource utilization, affective symptom evaluation, standard blood workup, neuroimaging evaluation with magnetic resonance imaging, and optionally, cerebral spinal fluid analysis and APOE genotype determination.

6.2 Results

Of all the four groups, the worst results in most areas were achieved by participants referred through diabetes clinics. Table 2 presents the results for the Slovenian cohort, namely a comparison of groups of participants who were included through family medicine clinics (N = 16) and diabetes clinics (N = 18). Individuals with diabetes achieved lower results in most of the tested areas, and these differences were statistically significant at MMSE ($p < 0.001$). The difference in cognitive function was also detected with the Repeatable Battery for the Assessment of Neuropsychological Status test battery (RBANS) ($p = 0.051$). Interestingly, patients from diabetes clinics reported lower anxiety ($p = 0.004$) and depression ($p = 0.072$). Nevertheless, the average anxiety and depression scores for both groups were within normal limits, suggesting that there are no clinically significant mood disorders in our sample. The same can be concluded with regard to frailty in both groups. Cerebrospinal fluid biological markers of dementia (Tau, PTAu, Aß42, Aß40 and 10x Aß42/40) show that the groups did not differ in the cerebrospinal fluid characteristics of dementia. In the group of participants referred through diabetes clinics, a higher proportion was diagnosed with MCI or dementia (83% vs. 63%). Similarly, a high prevalence of cognitive impairment was reported in the Spanish MOPEAD diabetes cohort (53), with 87.2% of participants having MCI and 7.7% AD. We can conclude that the groups differ significantly in cognitive functioning, and based on current results, these differences cannot be explained by the presence of vascular or neurodegenerative processes. One possible explanation would be that differences in cognition are affected by diabetes.

Table 2: Comparison of descriptive statistics of two groups of participants from family medicine clinics and diabetes clinics.

	Family medicine clinic	Diabetes clinic	p
N	16	18	
Age, M (SD)	73.9 (43)	73.5 (5.7)	.807
Years of education, M (SD)	12.7 (2.4)	12.2 (3.0)	.588
Frailty, M (SD)	3.3 (1.8)	3.8 (1.5)	.564
Anxiety, M (SD)	7.1 (3.9)	3.5 (2.2)	.004
Depression, M (SD)	4.9 (3.0)	3.2 (2.1)	.072
MMSE, M (SD)	27.9 (1.4)	25.6 (1.9)	.000
RBANS, M (SD)	90.5 (14.2)	81.7 (8.1)	.051
BMI, M (SD)	32.6 (9.1)	30.6 (4.8)	.458
MRI, Fazekas, Deep	1.00 (0.6)	1.33 (0.7)	.187
Tau [pg/ml]	412.9 (150.1)	424.7 (248.8)	.915
Ptau [pg/ml]	67.7 (23.7)	69.0 (32.0)	.932
Aß42 [pg/ml]	990.4 (375.5)	1144.4 (359.4)	.456
Aß40 [pg/ml]	14,682.7 (3,362.8)	14,850.5 (7,628.5)	.957
10x Aß42/40	0.7 (0.2)	0.9 (0.3)	.225

Legend: Frailty – Result on the Edmonton Frail Scale (0–17 points); Anxiety – anxiety subgroup score on the Hospital Anxiety and Depression Scale (0–21 points); Depression – depression subgroup score on the Hospital Anxiety and Depression Scale (0–21 points); MMSE – Mini–Mental State Examination; RBANS – The Repeatable Battery for the Assessment of Neuropsychological Status; BMI – body mass index; MRI – magnetic resonance imaging; FAZEKAS – visual assessment of white matter vascular lesions (0–3); Aß42 – amyloid beta 42; Aß40 – amyloid beta 40; Aß42/20 –amyloid beta 42/40 ratio.

7 Conclusion

Recognizing the increasing incidence of diabetes and dementia is crucial for appropriate, timely, and quality treatment of patients. Many common risk factors and their interactions are important in the clinical practice of a family medicine specialist, diabetologist, neurologist or other specialist treating such a patient, and it is crucial to identify them early and treat them appropriately. Cognitive assessment of patients with diabetes is vital for the appropriate choice of pharmacological and non-pharmacological treatment.

Conflict of interest

None declared.

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