Original Research

Cognitive decline and diabetes in the clinical setting

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Abstract

Objective. The aim of our study was to evaluate the prevalence of cognitive decline in patients with diabetes in the clinical setting and to identify patient characteristics directly associated with this condition.

Methods. In our cross-sectional study, we applied the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) to determine cognitive function in 172 diabetic patients, in the clinical setting. We included 120 patients with type 2 diabetes (T2DM), 42 cases with type 1 diabetes (T1DM) and 10 patients with confirmed secondary diabetes (SDM). The mean age of the participants was 62.4 years (±1.01, min: 26 years, Max: 87 years), with median diabetes duration of 15±11.8 years.

Results. More than half (55.23%) of the subjects presented cognitive deterioration, which was diabetes type-specific ($p<0.05$). Mild forms affected mostly T1DM and SDM cases (31.5% and 30% vs. T2DM: 14.5%, $p=0.00$), whereas moderate cognitive decline was more predominant in T2DM (21.9% vs. T1DM: 7.1%, $p=0.1$). A higher prevalence of severe cognitive impairment was present in T1DM (14.5% vs. T2DM: 8.7%, $p=0.1$).

The middle-aged category (40-64 years) was characterized by a more significant reduction of cognitive function in comparison with other age groups ($p=0.02$).

No gender-related difference in the prevalence of cognitive decline was found (female: 45.83% vs male: 45.71%, $p=0.98$), although severe forms were significantly more suggestive for men (15.27% vs. 4.18%, $p=0.04$).

Diabetic ketoacidosis (DKA) at admission was more frequently associated with cognitive deterioration, in comparison with hypoglycemic events ($p=0.03$).

In T2DM, cognitive decline ($p=0.006$, $r=-0.342$) was associated with the presence of anemia.

In T2DM women, treatment with calcium-channel blockers facilitated cognitive decrement ($p=0.01$, $r=-0.339$), whereas in men, therapy for distal symmetric polyneuropathy resulted in higher MMSE/ MoCA test scores ($p=0.00$, $r=0.72$).

In T1DM, a higher glycemic burden evidenced by increased HbA1c ($p=0.03$, $r=-0.364$) and glycemia at admission ($p=0.01$, $r=-0.389$) was suggestive to a more severe form of cognitive impairment. Distal symmetrical polyneuropathy ($p=0.05$, $r=-0.305$) and diabetic retinopathy ($p=0.03$, $r=-0.102$) was often co-occurring with cognitive decline.

Cognitive deterioration was associated with insulin therapy ($p=0.05$, $r=-0.232$).

Conclusion. The prevalence of cognitive decline is high in the diabetic population. Risk stratification must start at diagnosis and physicians should follow disease progression periodically, with special attention attributed to T1DM and the middle-aged population.

Keywords: diabetes, cognitive dysfunction, middle aged, disability

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Background & Aims

Since 1980 the global prevalence of diabetes has increased at an alarming rate. The International Diabetes Federation (IDF) estimates that by 2030 the number of diagnosed cases will reach up to 643 million worldwide [1]. Advances in treatment opportunities targeting cardio-renal-metabolic protection, the implementation of cutting-edge technology (continuous glucose monitoring systems, insulin delivery systems), along with timely screening and management of diabetes-related complications have considerably increased life expectancy [2-5]. Consequently, the timeframe in which disability might intervene in diabetes disease progression has been prolonged. The risk for a diabetic person to develop any kind of impairment during the course of the disease is 50-90% higher, compared to the non-diabetic population [6].

Disability in diabetes is multidimensional and of a progressive nature. It represents the cumulative effect of comorbidities (obesity, arterial hypertension, dyslipidemia), combinations of macro- (coronary heart disease, stroke, peripheral arterial disease) and microvascular complications and its consequences (end-stage renal disease, blindness, diabetic foot and amputations). It also includes diabetes related burden and distress [7,8]. Due to the improved management of the aforementioned associated comorbidities, recently the attention has been directed towards the possible impact of other, "non-traditional" diabetes-related conditions, such as cognitive decline.

Cognitive decline is also a determinant factor in the development of disability in diabetes, leading to diminished quality of life [9].

Diabetes-associated cognitive decrement is an early, minor change which can appear even from the prediabetic stage. It is characterized by slow progression of memory loss, limitations of executive function or processing speed [10].

Moderate cognitive impairment affects one or more cognitive domains such as learning, mental flexibility, executive function, attention, memory, but it does not prevent patients from pursuing daily activities or diabetes related self-care tasks. Identification at this stage is crucial for delaying further progression [10].

Dementia risk is 1.5-2.5-fold higher in type 2 diabetes, both of vascular and neurodegenerative etiology, affecting several cognitive domains, by which the ability to pursuit daily self-care and self-monitoring behaviors is diminished, resulting in poorer prognosis [11].

In the clinical practice, early or middle stages of these conditions are frequently unrecognized or neglected [11]. Financial and psychosocial implications are enormous not only on the individual, but also on a populational level [12]. The aim of this study is to highlight the increasing burden of cognitive decline of the diabetic patient in the clinical setting and to identify patient characteristics which are in direct link with these conditions.

Methods

Study population

We conducted a cross-sectional study on 172 patients at the Clinic of Diabetology, Department of Internal Medicine, Emergency Clinical County Hospital, Târgu Mureș, Romania between March 2021 - March 2023. The diagnosis and type of diabetes had been previously confirmed using the 2023 version of Standards of Care of the American Diabetes Association (ADA) [13]. According to this, we distinguished 3 major clinical entities: type 2 diabetes (T2DM), type 1 diabetes (T1DM) and secondary diabetes (SDM). The etiology of SDM consisted of chronic pancreatitis or an acute exacerbation of chronic forms.

Inclusion criteria were: patients aged >18 years in a stable physical and mental state, who were not previously diagnosed with any form of cognitive impairment, without any medication which could interfere with cognitive or mental functions, who understood and spoke the language used by the investigator, and who consented to participate. Patients who were suffering from acute critical illness, chronic pain, severe psychiatric conditions that would affect the evaluation, blindness, deafness or in an unstable cardiorespiratory or vegetative state were excluded from the study.

Demographic data and laboratory tests

Baseline data of the subjects were collected, including: gender, age, residence, circumstances of hospital admission (emergency or scheduled visit), body mass index (BMI), abdominal circumference (AC), smoking and alcohol consumption. We revised the patients' medical charts and included family medical history of diabetes mellitus (DM), cardiovascular disease (CVD) and malignancies. Personal medical history of diabetes duration, the presence of macro- and microvascular complications (retinopathy, nephropathy, peripheral polyneuropathy, history of amputation) were also noted. Medication history was reviewed not only for oral and injectable antidiabetic treatment and insulin therapy, but also antihypertensive, antihyperlipidemic agents and distal peripheral polyneuropathy treatment.

Routine laboratory tests from venous samples were performed, including: complete blood count, metabolic status: fasting plasma glucose, glycemia on admission and discharge, hemoglobin A1c (HbA1c), lipid profile: triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), uric acid, liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, renal function: creatinine, urea, GFR (calculated by the CKD-EPI equation), urinary albumin to creatinine ratio (UACR) and screening for thyroid dysfunction: thyroid stimulating hormone and free thyroxine (TSH and FT4) levels.

Individual interview and screening tools

The study was approved by the Ethics Committee of the Emergency Clinical County Hospital of Târgu Mureș. Patients who met the inclusion criteria and signed the informed consent form before starting the assessment.

Participants were informed about the study procedure by the investigator. The investigators, 4 previously trained medical residents offered guidance at the beginning of the screening and were available to answer questions during the test. Depending on the language spoken by the patient we applied the Romanian or the Hungarian versions of the questionnaires. The duration of the test was between 5 to 10 minutes. To respect patient's privacy, it was carried out in a separate consulting room during hospital admission.

To examine overall cognition, we used two validated screening instruments the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Both tests are widely used in the clinical setting and for research purposes worldwide, due to their accessible implementation [14]. MMSE explores orientation, immediate short-term memory, language functioning and attention, but lacks the determination of executive function, which is essential when complex diabetes-related tasks need to be carried out. For this, we considered using the MoCA test in the elderly population (>65 years), in which executive function loss is more prevalent [15-17]. The maximum score was 30 points for each test. We categorized our patients in conformity with MMSE test scores below the age of 65 and using MoCA test results above 65 years. For MMSE: ≥24 points stated normal function, 19-23 points mild, 10-18 points moderate and ≤9 points indicated severe cognitive decline. For MoCA test: a score of ≥26 indicated normal status, 17-25 points mild cognitive impairment, 10-16 points moderate cognitive impairment, while <10 stood for severe cognitive function loss [15,16].

Statistical analysis

Descriptive statistics for continuous numeric variables were carried out and represented as means and standard deviations (SD) for parametric variables and median (min, Max) for non-parametric variables. For categorical variables absolute or relative frequencies (%) were calculated. The Kolmogorov-Smirnov test was conducted to assess normality of data. Student's t-test for parametrical and Mann-Whitney test for non-parametrical distribution of data was used to compare numerical data.

Categorical data were assessed using the Fisher's exact test. In all cases we used two-tailed tests, and p-values were considered significant if ≤ 0.05. Statistical data analysis was performed by using IBM SPSS Statistics 25.0 software.

Results

In our study population 50.5% were female, the mean age of the participants was 62.4±1.01 years (min: 26 years, Max: 87 years), with a median of diabetes duration of 15±11.8 years. Out of the examined cases, 120 subjects (69.8%) were previously diagnosed with T2DM, 42 (24.4%) with T1DM and 10 cases (5.81%) had confirmed SDM. More than half (53.4%) of the patients were rural residents and 20% of the cases were admitted via the Emergency Medicine Department. Family medical history of the investigated subjects included DM in 47% of the cases, CVD in 44%, and history of neoplastic diseases in 14.5% of the cases. *General patient characteristics* are shown in table I, clinical and laboratory parameters are represented in table II.

Table I. General characteristics of the studied population.

	Type 2 diabetes (n=120)	Type 1 diabetes (n=42)	Secondary diabetes (n=10)
Age (Mean ± SD)	66.1±0.98	52.9±2.18	57.9±5.04
Female (nr/ %)	66 / 55	18 / 42.8	3 / 30
Rural residence (nr/ %)	69 / 57.5	21 / 50	4 / 40
Admission via emergency department (nr/ %)	21 / 17.5	10 / 23.8	4 / 40
Diabetes duration (years± SD)	15.4±11.7	16.53±12.07	4.9±7.47

Table II. Clinical and laboratory metabolic parameters of diabetic patients (mean± SD).

	Type 2 diabetes	Type 1 diabetes	Secondary diabetes
BMI (kg/m²)	31.5±5.52	23.9±4.59	22.18±3.26
AC (cm)	108.9±1.37	87.5±2.46	91.28±3.66
HbA1C (%)	9.05±2.17	10.02±2.64	10±3.4 0.46
Glycemia at admission (mg/dl)	233.4±91.69	245.46±114.16	235.5±98.53
Glycemia at discharge (mg/dl)	129±38.03	180±69.02	191.4±87.0
Total cholesterol (mg/dl)	177.8±75.8	173.1±35.7	173.3±56.7
LDL-cholesterol (mg/dl)	176.7±82.4	102.06±24.8	82.3±17.4
HDL-cholesterol (mg/dl)	48.27±12.6	48.91±6.97	53.55±26.09
Non-HDL cholesterol (mg/dl)	119.4±43.5	135.9±27.2	85.95±25.3
**Triglyceride (mg/dl)	254.1±263.2	113±51.3	217.4±286.6
Uric Acid (mg/dl)	6.04±1.82	4.61±51.3	5.74±2.42

*BMI: body mass index, AC: abdominal circumference, HbA1c: hemoglobin A1c, LDL: low- density lipoprotein, HDL: high- density lipoprotein; *p<0.05, **p<0.01*

Table III. Cognitive test results and severity of cognitive decline in different types of diabetes.

	Type 2 diabetes	Type 1 diabetes	Secondary diabetes
***MMSE (nr: 88)**	23.04±9.68	21.2±9.45	23.2±9.52
*Mild (%)	5.66	20.7	26.5
Moderate (%)	15.5	3.57	0
Severe (%)	6.49	10.2	0
***MoCA (nr: 84)**	24.37±8.78	22.5±0.7	24.5±8.58
*Mild (%)	8.62	10.8	2.5
Moderate (%)	6.4	3.57	0
Severe (%)	2.3	4.08	0

*MMSE: Mini- Mental State Examination, MoCA; Montreal Cognitive Assessment; *p<0.05*

As far as the *chronic complications* of diabetes are concerned, diabetic polyneuropathy appeared to be the most frequent microvascular complication, regardless of the type of DM (diabetic polyneuropathy prevalence: T2DM: 68.3%, T1DM: 57.1%, SDM: 50%, p=0.69). Mönckeberg medial sclerosis (MMS) was statistically more prevalent in T2DM, present in half of the investigated cases (MMS prevalence: T2DM: 50% vs. T1DM: 26.1% vs. SDM: 30%, p=0.01). Prevalence of amputations was also significantly higher in this group (amputation prevalence: T2DM: 13.3% vs T1DM: 2.3%, p=0.03). Diabetic retinopathy was significantly more common in T1DM (diabetic retinopathy prevalence: T1DM: 33.3% vs T2DM: 18.3% and SDM: 20% p=0.04). Chronic kidney disease was found to be present in one third of the T2DM and SDM cases and in 21.4% in T1DM, without statistically significant difference between the groups (p=0.56).

Surprisingly, more than half (55.23%) of the included subjects presented some degree of *cognitive deterioration.* Cognitive function loss was diabetes type-specific (p<0.05), as shown above in figure 1. Mild cognitive function loss affected T1DM and SDM patients significantly, accounting for approximately one third of the investigated cases (31.5% and 30% vs. T2DM: 14.5%, p=0.006). In T2DM, its prevalence below 65 years of age was significantly lower, as stated in table III, (5.6% vs. T1DM: 20.7% and SDM 26.5%, p<0.001). Moderate impairment was more frequent in T2DM, independent of the age category (21.9% vs. T1DM: 7.1%, p=0.19). In general, cognitive decline was present in a higher degree in T1DM, with reduced MMSE and MoCA scores in this category, almost reaching statistical significance (p=0.06). Also here, severe forms of cognitive decline appeared more frequently (14.5% vs. T2DM: 8.7%, p=0.19), but without statistical significance.

In our study population, subjects with SDM presented only mild forms of impairment.

Figure 2 illustrates the cognitive status in different age groups. Age categories were represented, as follows: 18-39 years: 5.81%, 40-64 years: 45.3%, 65-74 years: 25.5%, 75+ years: 23.2%.

In the middle-aged (40-64 years) and old population (>75 years), all four stages of cognitive status were represented. Ageing predisposes to cognitive deterioration (p=0.00), also a major decline was found in middle-aged adults (40-64 years) in comparison with other age categories (p=0.02). In this age group, nearly half of the examined cases (48.6%) had cognitive decline.

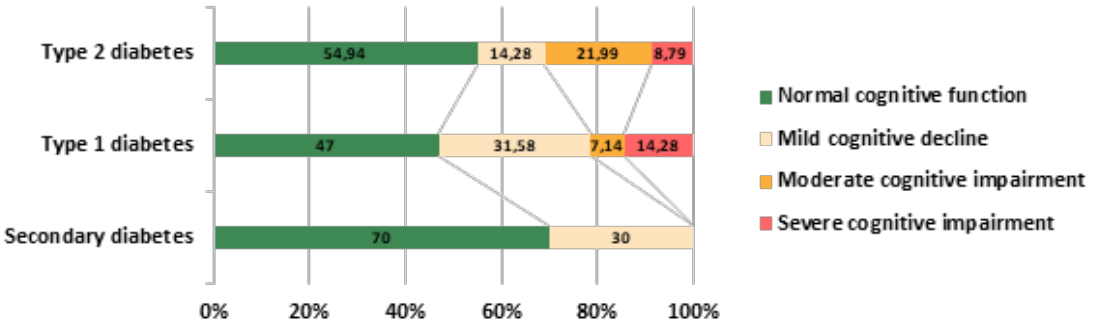

Figure 1. Cognitive decline in different types of diabetes.

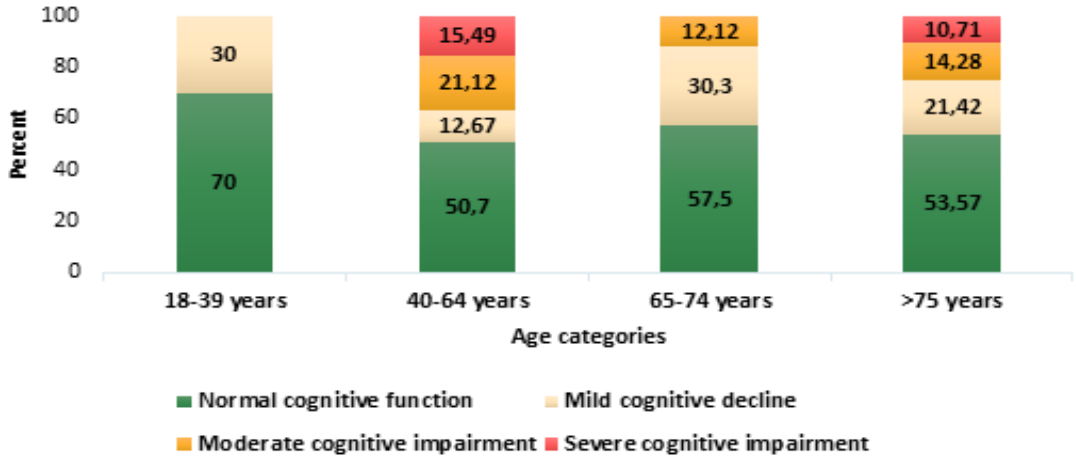

Figure 2. Cognitive function in different age categories.

Moderate function loss appeared to be frequent (40-64 years: 21.12% vs. 65-74 years: 12.12% and 75+ years: 14.28% p=0.07) and severe cognitive decline (p=0.02, OR=4.33, CI 1.156-16.28) was significantly more prevalent in the middle-aged category, compared to the rest of the age groups. In addition, 78.5% of the patients suffering from severe cognitive function loss were middle-aged.

In our study population, there was no gender-related difference regarding the prevalence of cognitive decline (female: 45.83% vs. male: 45.71%, p=0.98). Analyzing the severity of cognitive decrement, we found that severe forms of cognitive decline were significantly more frequent in men (15.27% vs. 4.18%, p=0.04). Interestingly, in women the presence of distal sensory polyneuropathy (p=0.04, r=-0.2) was correlated with more severe forms of cognitive impairment.

Fluctuating glucose levels preceding hospital admission, both hypo- and hyperglycemic events, were present in 17.44% of the cases.

Only a minor proportion (5.81%) of all cases investigated was admitted for repeated *episodes of hypoglycemia*. Half of the cases were of medium severity (<54 mg/dl), 30% required admission for altered mental or physical status which needed assistance for treatment, documented as severe episodes and 20% were admitted with mild forms of hypoglycemia (<70 mg/dl but ≥ 54 mg/dl). Patients with hypoglycemic events were often women (80%), with a mean age of 66.2 (± 16.2 years, min: 32 years, Max: 82 years), mostly of urban provenience. Most of the cases (70%) were suffering from T2DM with a disease progression of more than 15 years using insulin therapy or insulin combined with other oral antidiabetic agents (Metformin, Sodium-glucose cotransporter 2 (SGLT2) inhibitors or Glucagon-like peptide -1 (GLP-1) agonists). There was no significant difference between the results achieved at cognitive testing in this group, in comparison with the rest of the participants (MMSE: 27.87±2.58 points, MoCA:22.3 ± 2.2 points, p=0.13). One third of the cases admitted for hypoglycemia suffered from minor cognitive decline.

Hyperglycemic metabolic dysregulation was represented in almost half of the cases (47.67%). Diabetic ketoacidosis was found in 13.37% and hyperosmolar hyperglycemic state in 1.12% of all subjects included. Mean age of the patients admitted for diabetic ketoacidosis was 54.14 years (±15.6, min 26, Max 85), represented by T1DM and T2DM cases equally. In these cases, diabetes duration was prolonged (more than 15 years), patients were on insulin treatment, in T2DM frequently combined with SGLT-2 inhibitors. Half of the diabetic ketoacidosis cases suffered from some degree of cognitive decline. Compared to the patients suffering from hypoglycemic event on admission, those admitted for diabetic ketoacidosis had a statistically significant decline in cognitive function (MMSE score for ketoacidosis cases: 21.8±8.96 vs MMSE score for hypoglycemia cases: 27.87±2.58 points, p=0.03). Minor cognitive deficit was present in 61.5%, moderate decline in 15.5% and severe cognitive decline in 23% of the cases. Patients with cognitive decline and diabetic ketoacidosis had a mean age of 56.25 ± 15.9 (p=0.98), were mostly men (58%), from the urban area, mainly suffering from T1DM (65%) with long disease progression.

In T1DM patients, an *inadequate glycemic control* prior to admission influenced cognitive function to a greater extent, compared to other types. Subjects with a higher glycemia at admission (p=0.01, r= -0.389) and a higher HBA1c (p=0.03, r=-0.364) were shown to have a more pronounced cognitive function loss. Additionally, in this group significant correlations were observed between cognitive decline and the presence of distal symmetrical

polyneuropathy (p=0.05, r=-0.305) and diabetic retinopathy (p=0.03, r=-0.102).

In T1DM men, a *higher BMI* appeared to be protective, whereas in women, this was suggestive to a more severe cognitive decline (men: p=0.01, r=0.483; women: p=0.005, r=-0.354). Lastly, in T1DM women *beta blocker therapy* led to lower scores on cognitive tests.

In subgroup analysis of T2DM cases, significant correlation was found between cognitive impairment and the presence of *anemia* (p=0.00, r=-0.342). In women, where *calcium-channel blockers* were part of the treatment plan, cognitive decline appeared to be significantly more frequent (p=0.01, r=-0.339). In men, we found that *distal sensory polyneuropathy treatment* with B-vitamin complexes/gabapentin/selective serotonin reuptake inhibitor (SSRI)/alfa-thioctic acid or their combinations, resulted in the achievement of higher scores on the MMSE/ MoCA tests (p=0.00, r=0.72).

Regarding *diabetes treatment,* cognitive deterioration was associated with the use of insulin therapy (p=0.05, r=-0.232), 57.1% of the patients suffering from severe cognitive impairment was insulin treated. Contrary, the use of biguanides was more frequent in those with preserved cognitive function.

In secondary diabetes, the presence of peripheral arterial disease was associated with cognitive decline (p=0.04, r=-0.707).

As from laboratory findings, hyperuricemia was correlated with cognitive impairment. (p=0.03, r=-0.346). There was no statistically significant correlation between the presence or severity of cognitive decline and the circumstances of hospital admission (emergency department/ scheduled visits), diabetes duration, lipid profile, HbA1c, liver enzymes, thyroid function (p>0.05).

Discussion

To our knowledge this is the first article which describes the prevalence of cognitive disorder in both T2DM, T1DM and SDM using individual assessment in the clinical setting, in Romania.

According to Capisizu et al., 25% of individuals above 60 years of age in Romania suffer from dementia, with a maximum prevalence of 41.2% above 90 years, followed by a 33.3 % prevalence between 60-64 years of age, which far exceeds the Central European general rates reported by Cenko et al. in 2021 [18,19].

Data about cognitive function loss in the diabetic population vary, mainly depending on different geographical zones, the included population's baseline characteristics, study design and differences in testing modalities. Among T2DM patients the prevalence of cognitive decline is reported to be between 24.4% and 63.8% [20,21], for middle-aged T1DM patients (mean age 49 years) it is between 28% to even 71.42% for mild cognitive impairment [22], which is in concordance with our results. There were no available data about cognitive deficit in secondary diabetes.

In the medical literature, in the clinical setting, most T2DM cases were investigated regarding the severity of cognitive function loss. MMSE test scores indicated mild (92%) or moderate forms (8%) of cognitive deterioration [23]. In comparison, in our study population we found a lower average MMSE score (T2DM: 23.37±9.62 vs 25.49±3.52, T1DM: 21.87±9.96 vs 25.39±3.17), a lower prevalence of mild cognitive deficit and higher percentage of moderate and severe forms below the age of 65 years. This can be explained by the higher mean age of our study population (66.1±0.98 years vs 58.37±13.40 years), with a much longer diabetes duration (15.4±11.7 years vs. 8.69±5.88 years) and a higher prevalence of distal symmetrical polyneuropathy (68.3% vs. 63.4%), chronic renal disease (30% vs. 18.3%), peripheral arterial disease (25% vs. 13.73%) and arterial hypertension (92.5% vs. 74.51%) [23].

In the Study of Longevity in Diabetes (SOLID) published in 2022, authors executed factor analysis on several cognitive domains, according to diabetes type. This study confirmed our results, stating that older subjects (mean age: 68 years) with T1DM in comparison with T2DM achieved lower scores regarding several cognitive domains, which remained significant, even after adjusting for micro- and macrovascular complications, depression and sleep quality [24]. These results can be justified by the early onset of T1DM, intensive insulin therapy from diagnosis, higher glycemic burden during the lifespan, higher prevalence of both acute and chronic complications, factors which can be found in the general characteristics of our T1DM patients, too [25,26]. In T2DM compared to non-diabetic subjects an inferior performance in several cognitive domains was observed, but in the fully adjusted model just the visual episodic memory remained significantly altered, showing a more minor change [24].

Ageing is stated to be an independent factor of cognitive decline; thus, our findings suggests the existence of several other additional risk factors, which may lead to an acceleration of dementia risk in the middle-aged "still active" population. Still, our result are influenced by the higher number of participants in this age category [27]. The presence of diabetes in midlife accounts for a 19% increase in cognitive decline over the next 20-year period, compared to non-diabetic subjects, reported by a large community-based prospective cohort study published in 2014 by Rawlings et al., drawing attention to the fact that this population needs the practitioner's distinct attention [28].

Globally, the incidence and prevalence of dementia is higher in women [29], although we did not find significant gender-related differences in the prevalence of cognitive function loss. Different biological factors (sex hormones),

genotype, health determinants such as cardiovascular risk and psychosocial factors (education level) can contribute to gender related differences [30].

In our study, diabetes duration was not in a linear association with cognitive decline. This observation was previously described in 2021 by the U-shaped dementia risk after diabetes diagnosis, in a German cohort study [31].

Most studies on DKA and cognitive decline were carried out including T1DM children, adolescents or in animal models. Findings from the Study of Longevity in Diabetes highlighted that the increasing number of DKA episodes, leads to the progression of global cognitive decline affecting adults too, as evidenced by our results. Moreover, findings support also that DKA is a risk factor for Alzheimer's dementia in T2DM [32,33].

In our study, hypoglycemic episodes were represented by primary isolated minor or mild forms, after which cognitive function is usually fully restored within 1 hour. Even in severe forms of hypoglycemia a total and rapid recovery is observed after glycemic control is obtained, highlighting that in our study subgroup minor forms of cognitive decline was not caused by the acute hypoglycemic event [34].

Central abdominal obesity predisposes to a more accentuated cognitive decline in T2DM men and T1DM women, which is in concordance with the finding of a ten-year, population-based cohort study. This states that in the presence of abdominal obesity in diabetes, even mild hyperglycemic excursions can lead to an accelerated cognitive decline [35]. Although, in T1DM men abdominal obesity appeared to be protective against cognitive decline, which needs further elucidation.

We found an association between cognitive decline and anemia, this being a modifiable risk factor of dementia previously described by Choi JW et. al in a nationwide population-based cohort study in 2020, even in newly diagnosed T2DM patients [36].

Insulin therapy was associated with cognitive deterioration, which can be explained by the baseline characteristics of our subjects (older age, longer diabetes duration, poor glycemic control). Insulin treatment was shown to be used more frequently in severe cognitive decline, because of the higher prevalence of severe forms of cognitive decrement in T1DM. Biguanides play a central role in combating insulin resistance, one of the main mechanisms in dementia in diabetes. For this, long-term, high dose metformin therapy, which was present in our T2DM patient's treatment plan too, was demonstrated to be beneficial against cognitive decline [37].

Antihypertensive agents constitute a crucial part of the diabetic patient's treatment plan. A 5-year long prospective, population-based study of dementia epidemiology using data from the Canadian Study of Health and Aging (CSHA) described the indisputable role of calcium-channel blockers in cognitive decline [38]. Considering beta-blocker therapy, results are contrary, one study states that beta-1-selective beta-blockers were associated with worse cognitive capacity in patients with coronary artery disease, whereas data derived from a cross-sectional study, performed on 8,279 adults infirmed this hypothesis [39,40]. Our findings could offer a starting point to further analyses regarding the selection antihypertensive therapy and cognitive decline in diabetes.

In our observation, a higher serum uric acid (SUA) level was present in the patients who achieved lower scores on cognitive tests. These finding are in concordance with a large cross-sectional Chinese study carried out on 2,102 elderly subjects, which also has shown a linear decrease of cognitive performance in hiperuricaemia [41].

Some studies suggest cognitive function loss to be the fourth microvascular complication of diabetes due to its high prevalence, similar pathophysiologic background and its explicit associations with other well-known microvascular complications [42]. Suggestions have been made that identification of diabetic retinopathy would be an early predictor of cognitive decline [43]. Our findings describe the association between distal sensory polyneuropathy in both T1DM and T2DM patients with cognitive function loss, which can be justified by the release of higher concentration of neuron-specific enolase (NSE) from damaged neural cells from the periphery, which enters the dysfunctional blood-brain barrier and injures brain cells [44]. Neuroprotective effects of the medication used in polyneuropathy treatment could be a possible explanation for better cognitive test results.

Medical literature is scarce on secondary diabetes and cognitive function. We included this study subgroup as an individual entity, and even within this low number of subjects, correlations were found with peripheral artery disease and cognitive deficit. This is known to be a predisposing factor for cognitive decline independent of other cerebral or cardiovascular diseases [45].

Limitations of the study

This evaluation has potential limitations. First of all, we did not include information about educational level, social status, ethnicity, nutritional patterns which are all major determining factors of cognitive status [46,47]. Secondly, we included only a small number of participants in the SDM group, who had all the investigations required for the assessment. Although the prevalence rate of pancreatogenic diabetes (T3cDM) is between 5-10%, the number of participants included do not provide enough data to draw any kind of conclusion [48]. Thirdly, the high number of cases included in the middle-aged category might influence our results of the reported cognitive deficit rate in this category, yet our results are still unexpected. Lastly, a cross- sectional study design does not permit to draw statistically significant conclusions about the progression of cognitive decline.

Future perspectives for research might be the design

of an extended, multicenter research with expanded and identical number of subjects in each category of diabetes and age group. By this approach, standardized national databases could be formed and public health services could be informed about the current situation of cognitive impairment in diabetes in Romania.

Conclusion

We found a high prevalence of cognitive decline in the diabetic population in the clinical setting. In view of our results, early identification and risk stratification at diagnosis is essential to design a comprehensive care plan for each patient by identifying new glycemic targets, individualized monitoring and treatment strategies. Preventive measures, targeted complication screening, and psychosocial support may be required especially in T1DM where more severe forms of cognitive decline develops and in the middle-aged category, which appears to be more frequently affected. By addressing these issues, a more stable metabolic control can be achieved.

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