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Cognitive Frailty in Older Adults with Diabetes Mellitus: Bases for its Approach

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Abstract

The impairment of cognitive abilities, emotional control, learning, and mobility in older adults with diabetes mellitus constitutes a global socio-health problem given the high prevalence of the condition, its impact on the healthcare system and society, and the burden of suffering for those affected and their families. In this review, we highlight the problem, its causes, presentation, and natural history. We propose a prevention and treatment approach, as the older adult stage is characterized by its heterogeneity and the scarcity of resources. This is a call to raise awareness and consider aging as a process that is simply another stage of human life, and that this stage can be "healthy" or accompanied by pathological processes that affect the quality of life of the individual and their environment. It is important to consider the search for new strategies and resources to address this issue. We emphasize that diabetes is the most frequent metabolic problem in older adults, affecting 30% of them. All cells in the body, because they share basic mechanisms for nutrient utilization, are affected. The central nervous system consumes the most nutrients, making it one of the systems most affected. We have the opportunity to apply the body of knowledge developed to understand diabetes and the resources available to us. In this review, we provide an overview of these resources and their relationship to the prevention and treatment of this metabolic and neurological problem.

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Introduction

A confluence of related factors, changes in diet, sedentary lifestyle and population aging led to a rapid increase in the incidence of diabetes mellitus (DM), especially type 2 diabetes (T2D), a disease with an enormous burden in terms of health and economic consequences in the older adult (OA) population [1]. Since DM is a metabolic problem, all of a person's systems will be affected, especially the central nervous system (CNS), which is the main consumer of oxygen, calories, and building blocks [2]. As the population ages, T2D, cognitive impairment, and dementia are reaching epidemic proportions worldwide, making it increasingly important to identify methods to address this pandemic [3-5]. The prevalence of dementia among people with both type 2 and type 1 diabetes mellitus is estimated to be 6 to 14%, increasing with age, duration of diabetes, and elevated HbA1c levels [6-8]. Thus, diabetes doubles the risk of developing dementia [9]. Accumulating evidence shows that about one-third of cases of severe cognitive impairment could be delayed or prevented by managing diabetes comorbidities such as hypertension [10], sedentary lifestyle [11], obesity [12,13], tobacco and alcohol consumption [14], depression [15,16] and controlling the physiopathogenic mechanisms of DM, given by the excess of circulating lipids [17], and hyperglycemia [18,19]

Etiogenic Markers and Processes Leading to Tissue Damage

Hyperglycemia, HbA1c, insulin resistance (HOMAIR), systemic inflammation such as CRP, cerebral microvascular injury (neuroimaging), cerebral amyloid and tau proteins, brain-derived neurotrophic factor (BDNF), advanced glycation end products (AGEs), and adipokines [20,21].Neuroimaging reports on vascular brain lesions, particularly lacunae, hypotrophy especially of the white matter, enlargement of sulci and ventricles with hippocampal involvement. Neuropathological studies may report an increased burden of infarcts or microinfarcts, lacunae attributable to abnormalities in small cerebral perforating arterioles, such as arteriolosclerosis, lipohyalinosis, or fibrinoid necrosis. Human autopsy studies showing vascular abnormalities in people with diabetes mellitus (DM) lend strength to the findings of imaging studies [22]. Alzheimer's disease (AD) is the most common form of dementia in older adults, and T2D, due to chronic hyperglycemia and insulin resistance, constitutes a risk factor for AD, especially when considered as a syndrome [23]. Vargas Soria M et al. studied a murine model and, in their work, mention that while aging is the main risk factor for AD, evidence suggests that metabolic alterations such as T2D contribute significantly. A distinctive pathological event in Alzheimer's disease (AD) is the deposition of amyloid-β (Aβ) in the brain, either as amyloid plaques or around the leptomeningeal and cortical arterioles, constituting cerebral amyloid angiopathy (CAA). This is observed in 85–95% of autopsy cases of AD and contributes to AD pathology by limiting perivascular drainage of Aβ. Experimental data supported the relationship between the metabolic disease and Aβ deposition affecting vascular integrity, ultimately contributing to AD pathology and related functional changes in the cerebral microvasculature. [24]. Insulin resistance, neuroinflammation, altered cerebral glucose metabolism, oxidative stress, mitochondrial dysfunction, and amyloidosis are biological events found in neurological disorders. Altered insulin-mediated signaling and cerebral glucose hypometabolism are characteristic signs observed in the brains of patients with certain neurological diseases, but also others such as T2D and vascular diseases. These findings, based on significant reductions in insulin receptor autophosphorylation and Akt kinase activity, and increased GSK-3 activity and insulin resistance in these neurological diseases, contribute to the decline in cognitive function. Supporting this relationship is the fact that nasal and hippocampal insulin administration has been found to improve cognitive function [25]. A central feature of T2D is the alteration of insulin signaling, which causes insulin resistance. Thus, it not only affects systemic metabolism but also the brain by altering cerebral insulin pathways.Some autopsy studies have failed to demonstrate an association between T2D and the neuropathology of AD. However, the clinical presentation of brain damage from DM in older adults and from AD shows overlap, as some anatomopathological studies have shown. We emphasize that cognitive impairment in DM has pathophysiological characteristics specific to this disease and that there may be common factors [26]. Some autopsy studies found fewer neuritic plaques (NP) and neurofibrillary tangles (NFT) in the brains of diabetics [27,28] . Dos Santos M et al., when examining the association between diabetes and neuropathology of AD in 1,037 Brazilian AMs, also found no link between brain damage from DM and from AD [29]. We highlight the endoplasmic reticulum stress

mechanism and its association with mitochondria as responsible for metabolism. When an excess of these structures exceeds their metabolic capacity, endoplasmic reticulum stress is triggered. This stress can resolve itself or lead to mitotic pause, i.e., senescence, cellular apoptosis, or autophagy, with the consequent loss of cells and synapses. This affects neuronal circuits, leading to their loss and delamination in many cases [30-32] These facts give the person with DM a special vulnerability to neurodegeneration [33,34]. (Fig 1 and 2)

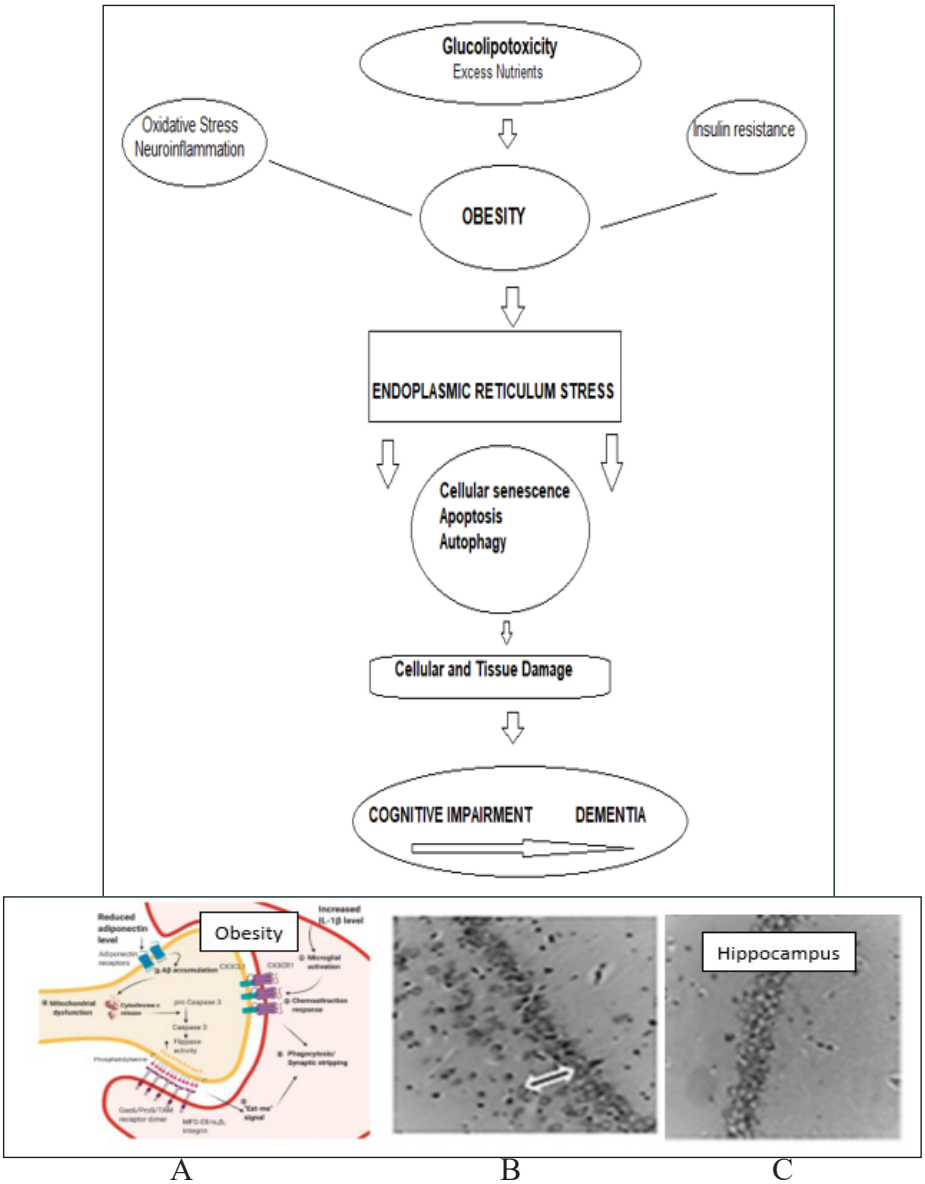

Figure 1: Pathophysiology of Cognitive Decline – Dementia in Older Adults with Diabetes Mellitus

A. Diagram: Excess nutrients trigger a complex metabolic alteration, where their storage, distribution, and biotransformation unleash a series of complications leading to endoplasmic reticulum stress at the cellular level, senescence, apoptosis, and/or autophagy, which will cause cell death and tissue damage [2].

B. Lipotoxicity causes intrinsic aberrant microglial activity in CNS cell populations, apoptotic spines that can trigger synaptic destruction. 1. The elevation of hippocampal IL-1β induced by a high-fat diet promotes the pro-inflammatory M1 phenotype in microglia. 2. Aberrant microglia are attracted to CX3CL1 (fractalkin) on the dendritic spine, which is recognized by microglial CX3CR1. On the other hand, 3. the reduction

in adiponectin levels induces the accumulation of β-amyloid in the hippocampus. 4. The accumulation of Aβ causes mitochondrial dysfunction with a reduction in mitochondrial membrane potential and an increase in oxidative stress. Apoptotic mitochondria release cytochrome c, which can activate flippase activity via caspase 3. 5. Phosphatidylserine, located in the outer membrane of the phospholipid bilayer, acts as an "eat me" signal, which is recognized by microglial receptors. 6. Aberrant microglial activity, such as neuronal mitochondrial dysfunction, triggers synaptic destruction by microglia [17]

C. Microscopy of the hippocampus at 40x magnification showing how synaptic alterations and cell death lead to delamination of the cell layers [30].

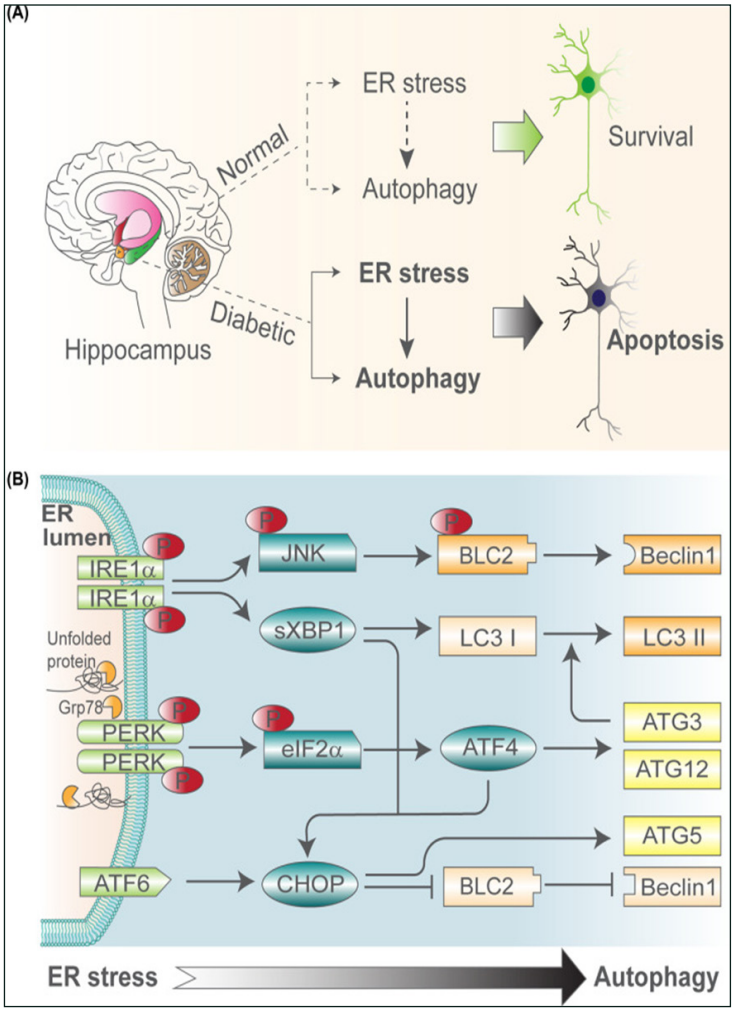

Figure 2: ER stress-autophagy axis regulates diabetes-related cognitive dysfunction.

(A) At normal state, hippocampal neurons survive with low levels of ER stress and autophagy, whereas in diabetes, unresolved ER stress further enhances autophagy and ultimately lead to apoptosis, and thus declines cognitive functions. (B) Cross-talk of ER stress-autophagy axis[31]

Diabetes and Frailty

DM, frailty, sarcopenia, and the association of pathologies share physiological mechanisms and pathological changes [35]. In older adults, the loss of muscle mass is accompanied by a relative increase in visceral fat; this is "sarcopenic obesity," closely related to insulin resistance and mitochondrial dysfunction. Low levels of testosterone and insulin-like growth factor are associated with insulin resistance, T2D, decreased protein synthesis, muscle mass, and frailty [36,37].

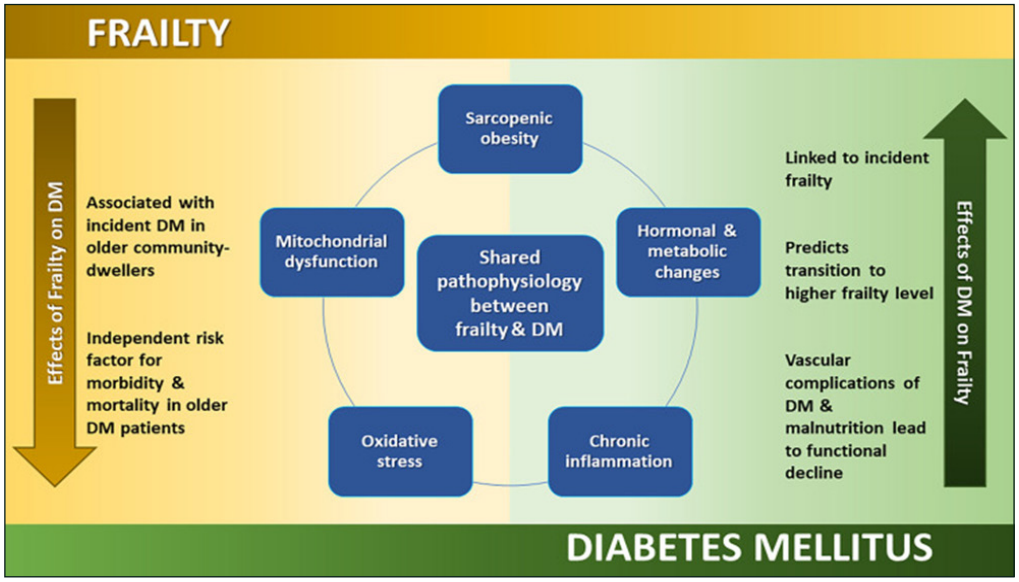

Figure 3: Diabetes and Frailty [37]

Addressing the Problem in the Clinic

From a geriatric and gerontological perspective, it is important to assess the impact of cognitive and metabolic disorders on functional status. This will allow us to refer the patient for studies that confirm the degree of impairment and plan their treatment [38]. Functional status or functional independence (FI) can be assessed using the Activities of Daily Living (Fig 3) [39,40].

Self-care activities
A. Eating
0 = No problem
1 = Independent, but slow or some spills
2 = Needs help to cut or pour; spills often
3 = Must be fed most foods
9 = Don't know
B. Dressing
0 = No problem
1 = Independent, but slow or clumsy
2 = Wrong sequence, forgets items
3 = Needs help with dressing
9 = Don't know
C. Bathing
0 = No problem
1 = Bathes self, but needs to be reminded
2 = Bathes self with assistance
3 = Must be bathed by others
9 = Don't know
D. Elimination
0 = Goes to the bathroom independently
1 = Goes to the bathroom when reminded; some accidents
2 = Needs assistance for elimination
3 = Has no control over either bowel or bladder
9 = Don't know
E. Taking pills or medicine
0 = Remembers without help
1 = Remembers if dose is kept in a special place
2 = Needs spoken or written reminders
3 = Must be given medicine by others
9 = Does not take regular pills or medicine **OR** Don't know

Figure 4: The Activities of Daily Living (ADL)

Factors such as education, environment, lifestyle, work activity, and interpersonal relationships influence the cognitive health of older adults. Cognitive reserve is part of the mechanisms that would explain personal differences in rates of cognitive decline. Clare L et al. explored the mediating effect of cognitive reserve on the cross-sectional association between lifestyle factors and cognitive function in

older adults using data from a population-based cohort of 2315 older adults without evident pathologies in the Cognitive Function and Ageing Study Wales (CFAS-Wales) cohort between 2011 and 2013. They concluded that the cross-sectional associations support the view that improving cognitive reserve can benefit cognition, and the maintenance of cognitive health can be favored by a healthy and active lifestyle in later life [41].

According to Taniguchi et al., FI is crucial for independent living in old age; its loss is associated with brain damage, cognitive and motor impairment, social isolation, death, and high healthcare costs [42]. Cognitive frailty in older adults with DM is associated with the coexistence of physical frailty and cognitive impairment, increasing the risk of dementia, disability, and dependence [43]. Frailty is prevalent in older adults with DM, with prevalence rates between 10.4% and 20.8% in different studies [44]. Frailty frequently coexists with cognitive impairment [45]. The Edmonton Frailty Scale (EFS) is a multidimensional, rapid, and widely validated tool that assesses nine domains: cognition, health, functionality, social support, medication, nutrition, mood, continence, and functional performance through 11 questions. With a maximum score of 17, it classifies older adults from "no frailty" to "severe frailty" [46] (Fig. 5). Cognitive function can be assessed clinically by observing the patient's orientation to time and place upon arrival at the consultation, including their ability to live independently. This assessment can be supplemented with specific tests: the Mini-Mental State Examination, the Clock Drawing Test, the Montreal Cognitive Assessment, the Cognitive Subscale of the Alzheimer's Disease Assessment Scale, the Verbal Learning Test, the Digit Span Test, the Boston Naming Test, the Tracing Test, and the Frontal Lobe Assessment Battery [47]. From the perspective of managing older adults with diabetes mellitus, three main groups can be identified [48]. This will allow us to understand the natural history of cognitive frailty and tailor our approach to managing older adults. Fig 5 Edmonton Frail Scale [46]

Questions	A	B	C	REQUIRE FOLLOW-UP
For each item choose one option in column A, B or C. Points are assigned based on the column. Items marked with an asterix are to be scored based on information from the patient only.*	A = 0	B = 1	C = 2	☑
1. Cognition				
a) Are you or your family concerned about new problems with your memory?	NO	YES		☐
b) Have you been diagnosed with dementia, Alzheimer's disease, or a major neurocognitive disorder?	NO	YES		
2. General Health Status				
a) In the past year, how many times have you been admitted to a hospital?	0	1–2	>2	☐
* b) In general, how would you describe your health? *(Select one)*	EXCELLENT VERY GOOD GOOD	FAIR	POOR	
3. Functional Independence				
With how many of the following activities do you **require** help? ☐ Meal Preparation ☐ Shopping ☐ Telephone ☐ Housekeeping ☐ Taking Medications ☐ Transportation ☐ Laundry ☐ Managing Money	0–1	2–4	5–8	☐
* **4. Social Support**				
When you need help is there someone who you can count on who is willing and able to meet your needs?	ALWAYS	SOMETIMES	NEVER	☐
5. Medication Use				
a) Do you use 5 or more prescription medications on a regular basis?	NO	YES		☐
b) At times have your forgotten to take your prescription medications?	NO	YES		
6. Nutrition				
Have you recently lost weight such that your clothing has become loose?	NO	YES		☐
* **7. Mood**				
Do you often feel sad or depressed?	NO	YES		☐
8. Continence				
Do you have a problem with losing control of urine when you don't want to?	NO	YES		☐
9. Functional Performance				
Does your baseline health now limit you in the following? ☐ Vigorous activities around the house ☐ Climbing stairs ☐ Walking several blocks	NOT LIMITED AT ALL	LIMITED A LITTLE	LIMITED A LOT	☐

Figure 5: Comprehensive Geriatric assessment of older adult with diabetes mellitus [48]

Health status grade	Physical and functional status of elderly patients with diabetes
Good Health (Group 1)	No comorbidity or has ≤2 non-diabetes chronic illnesses (including stroke, hypertension, stage 1–3 chronic kidney disease, osteoarthritis, etc.) and no ADL impairment and ≤1 IADL impairment
Intermediate Health (Group 2)	Three or more non-diabetes chronic illnesses (including stroke, hypertension, stage 1–3 chronic kidney disease, osteoarthritis, etc.) and/or any one of the following: (1) mild cognitive impairment or early dementia; (2) ≥2 IADL impairments
Poor Health (Group 3)	Any one of the following: (1) one or more chronic illnesses with limited treatments and reduced life expectancy (including metastatic malignancies, lung disease requiring oxygen therapy, end-stage renal disease requiring dialysis, and advanced heart failure); (2) moderate to severe dementia; (3) ≥2 ADL impairments; (4) residence in a long-term nursing facility

Natural History of Cognitive Affectation in Older Adults with Diabetes Mellitus

The different stages of cognitive dysfunction in MA should be considered a continuum [49,50]. El deterioro cognitivo puede dividirse en tres etapas diferentes, según la gravedad: deterioro cognitivo leve (DCL), deterioro moderado y demencia. El término disminución asociada a la diabetes se refiere a cambios sutiles en la función cognitiva, que pueden dar lugar a quejas cognitivas (normalmente expresadas sólo por el paciente), pero que no deberían afectar las actividades de la vida diaria ni el autocontrol de la diabetes [51,52]. Los cambios cognitivos sutiles pueden afectar a uno o varios dominios cerebrales. Cognitivo: velocidad de procesamiento, observado en la fluidez verbal, la función ejecutiva y la memoria de trabajo reciente y remota, capacidad de aprendizaje, reconocimiento de personas, orientación temporoespacial, en la esfera emocional: ansiedad, depresión en la esfera motriz disminución de la velocidad de la marcha, arrastrar los pies al caminar, caídas y tardiamente alteraciones de la deglución con broncoaspiración e incontinencia urinaria y fecal terminando en la postración. movilidad. Evaluación de la marcha, equilibrio, prueba del levántate y anda [53]. Probablemente estas alteraciones comiencen en la etapa prediabética y evolucionan lentamente a lo largo de años, a un ritmo 50% más rápido que el del envejecimiento cognitivo normal [54].

Cognitive impairment can be divided into three different stages, according to severity: mild cognitive impairment (MCI), moderate impairment, and dementia. The term diabetes-associated decline refers to subtle changes in cognitive function, which may lead to cognitive complaints (usually expressed only by the patient), but should not affect activities of daily living or diabetes self-management [51,52]. Subtle cognitive changes can affect one or more brain domains. Cognitive: processing speed, observed in verbal fluency, executive function, and recent and remote working memory, learning ability, person recognition, and spatiotemporal orientation; emotional: anxiety and depression; motor: decreased gait speed, shuffling, falls, and later, swallowing difficulties with aspiration and urinary and fecal incontinence, eventually leading to immobility. Assessment includes gait, balance, and the stand-up walk test [53]. These alterations probably begin in the prediabetic stage [50] and evolve slowly over years, at a rate 50% faster than that of normal cognitive aging [54].

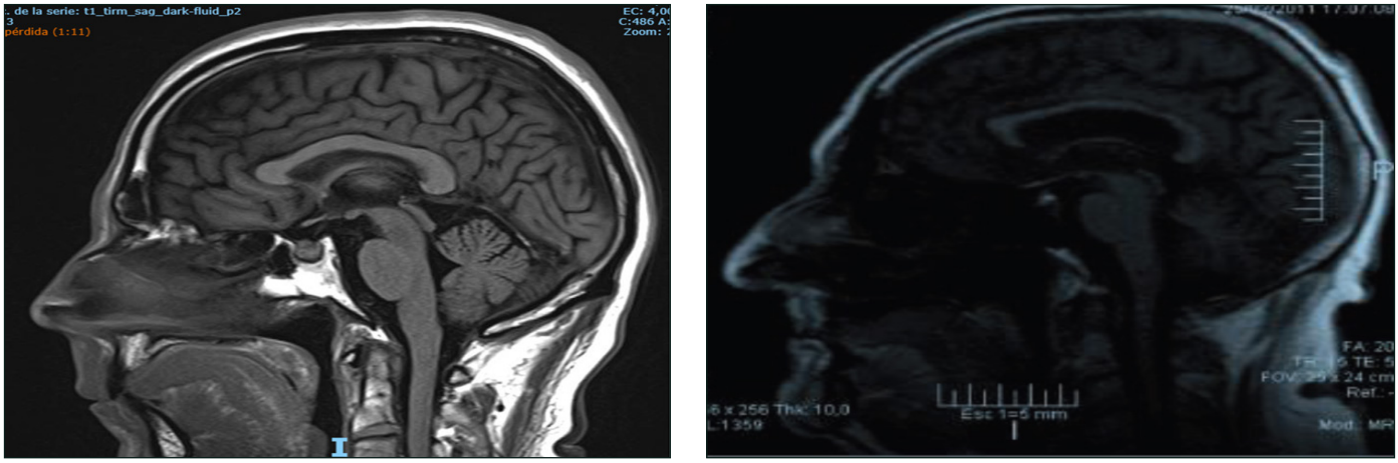

Figure 6: Natural History of Cerebral Involvement in Older Adults with Diabetes Mellitus

Brain Imaging Findings in Patients with T2D: The figure summarizes the findings from brain imaging studies in T2DM (for details and bibliographic references, see the text). The position of each imaging marker on the X-axis reflects the intensity with which it has been studied in relation to T2D. The position on the Y-axis reflects the extent to which a marker is affected in individuals with T2DM compared to controls, based on evidence from available studies.

Prediabetes

Marseglia A et al. studied 68 older adults (8.6%) with prediabetes and 45 (5.7%) without diabetes mellitus DM. The person will be in Group 1 of the Comprehensive Geriatric Assessment of Older Adults with Diabetes Mellitus [55]. The older adults with DM showed more pronounced impairment in perceptual speed and verbal skills, associated with progressive memory decline [56]. According to Wang X et al., a subgroup analysis revealed that the association between prediabetes and cognitive impairment was significant in women. Stratification analyses revealed that, in patients with prediabetes, triglyceride concentrations were negatively associated with cognitive function. Triglyceride control through lifestyle modification for prediabetes and adjunctive anti-inflammatory therapy specifically for diabetes may benefit cognitive performance. [57]. However, the study by Casagrande SS et al., based on the sample of older adults from the 2011-2014 National Health and Nutrition Examination Surveys, found no cognitive impairment in people with prediabetes, although it was found in those who had developed T2D [58].

Mild Impairment Stage (MCI) and Moderate Impairment

Cognitive declines associated with DM are subtle, not clearly affecting social or occupational functioning or DM self-control until advanced stages [59].Mild cognitive impairment, a prodromal stage of dementia, affects 20% of people aged 65 and over. The person will be in Group 1 of the Comprehensive Geriatric Assessment of AM with DM. It is estimated that one-third of these cases will progress to dementia within 5 years. And although both type 2 diabetes (T2D) and aging are very common processes, it has been established that T2D is a proven risk factor for dementia, almost doubling the risk of cognitive impairment. This allows us to recognize factors associated with cognitive decline such as insulin resistance [60], and hypercholesterolemia [61]. We highlight the work by Casagrande SS et al. based on the sample of older adults from the 2011-2014 National Health and Nutrition Examination Surveys, who found a clear association between hyperglycemia, obesity, dyslipidemia, hypertension, history of cardiovascular disease, stroke, and, to a lesser extent, depression, related to the development of T2D, unlike the non-moglycemic population. Cognitive function was assessed using the Consortium for Alzheimer's Disease Registry-Word Learning Test (CERAD W-L), the Animal Fluency Test, and the Digit Symbol Substitution Test (DSST). Older adults with diabetes showed mild cognitive dysfunction, as measured by the DSST, a sensitive measure of global cognitive function. The association ceased to be significant after adjusting for education. Previous research has shown that education level modifies the relationship between Alzheimer's disease pathology and cognitive function in older adults (29). However, in the overall

US population, with increasing HbA1c, a measure of average blood glucose levels over approximately three to four months, a significantly higher proportion of older adults with HbA1c ≥8.0% (≥64 mmol/mol) exhibited cognitive impairment, as measured by the DSST, compared with their counterparts with HbA1c <7.0% (<53 mmol/mol). Results from the CERAD W-L measure, a test of word learning and short-term memory, suggest that decreased glucose sensitivity may affect memory structures in the brain, including the hippocampus (4). The Longitudinal Study of Health and Retirement found that among adults ≥50 years of age, diabetes was associated with a 10% faster rate of memory decline, as measured by immediate and delayed recall of a word list. The CERAD analysis showed that verbal learning ability is compromised in individuals with diabetes, and the relationship of these changes to the hippocampus was identified. The importance of HbA1c was also highlighted, as it has diagnostic and prognostic value for diabetes mellitus and its associated comorbidities [46]. These findings have been corroborated by various epidemiological studies, such as those by Dove A et al., who emphasize the role of low-grade systemic inflammation, measured by C-reactive protein, sedentary lifestyle, and obesity [62]. The study of the association between diabetes in old age and hyperglycemia with the incidence of mild cognitive impairment and dementia [63]. The work of Ehrlich JR et al., who highlight the progression from mild cognitive impairment to dementia where all activities of daily living are lost, including the ability to recognize people, orientation, and mobility, leading to immobility [64]. These observations can be extrapolated to different populations, as demonstrated by the work of Mayeda Er, who studied this problem in older Mexican Americans with diabetes mellitus [65] and in the Chinese population [66-67], in the English population [68]. In The Edinburgh Type 2 Diabetes Study, the role of obesity in the diabetic population and the development of dementia is highlighted [69], to which we add the importance of abdominal circumference measurement, which indicates central obesity that is generally accompanied by low-grade systemic inflammation, as demonstrated by Yuan Y et al. [70] and Suemoto GK et al. in a population in Brazil. [71]. To which we must add that sarcopenia is independently associated with cognitive impairment and a higher risk of mortality from stroke or Alzheimer's disease compared to their healthy counterparts. Mobility, determined by the interaction of bone structure, brain muscle function, and balance associated with delayed memory, influences glycemic control and disease management in older adults with diabetes mellitus and is associated with an increased risk of falls [72]. Likewise, in older adults with DM, the presence of geriatric syndromes such as polypharmacy, immobility, pain, and mood disorders is increased [73]. To which we must add the danger of hypoglycemia associated with the alteration of regulatory mechanisms and the treatment of DM itself, which can cause damage due to lack of nutrients at the cerebral level or arrhythmias that cause ventricular fibrillation or trigger coagulation mechanisms generating emboli that cause stroke [74,75] (Fig. 7) The person will be in Group 2 of the Comprehensive Geriatric Assessment of Older Adults with Diabetes Mellitus, and all available resources will be used for their treatment.

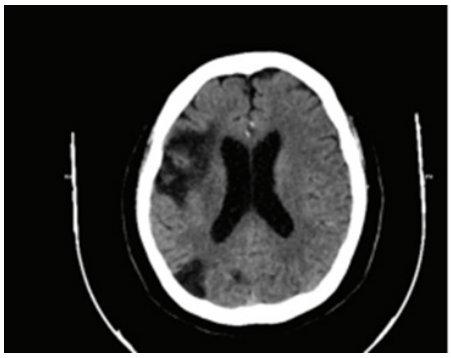

Figure 7: CT scan showing brain damage one month after an ischemic Stroke [75].

Established Dementia Stage

This stage corresponds to level 3 of the Comprehensive Geriatric Assessment of Older Adults with Diabetes Mellitus, loss of functional independence, and extreme frailty. Severe damage has already occurred in all systems, especially the central nervous system. Therefore, the person has lost their functional independence and is dependent for all activities of daily living, requiring assistance. Social support, especially from caregivers, is essential. From a clinical perspective, the goal is to achieve maximum comfort, prevent pain and dehydration due to diabetic polyuria by keeping blood glucose levels below 180 mg/dL, and prevent hyperosmolar coma. Efforts will be made to prevent pressure ulcers, aspiration pneumonia, falls, and fractures. Cell loss is progressive; the aim is to limit this loss through protein-rich nutrition.

Mobility

In older adults with diabetes mellitus (DM), mobility presents variations characterized by changes in gait speed and spatiotemporal characteristics, which are subsequently associated with cognitive impairment [76]. Understanding mobility impairment is important for recognizing its role in diabetes complications and preventing falls, fractures, and loss of functional independence. Herings et al. evaluated the relationship between gait characteristics derived from the Inertial Movement Unit (IMU) and cognitive function assessed using the Montreal Cognitive Assessment (MoCA)/Detailed Neuropsychological Assessment Battery (CANTAB) in middle-aged adults with and without uncomplicated T2D using multivariate linear regression and a neural network approach. Gait was assessed under conditions of (i) normal walking, (ii) brisk (maximal) walking, and (iii) dual-task cognitive walking (reciting alternative letters of the alphabet). Individuals with DM exhibited significantly slower gait speed in both slow and brisk walks and longer, more complex stride times during normal walking. When analyzing cognitive performance, the strongest association was observed between gait speed, global cognitive function (MoCA), and immediate/retarded memory performance and gait speed. This work demonstrated the impact of uncomplicated diabetes mellitus on gait speed and gait characteristics in midlife, and the relationship between gait characteristics, global cognitive function/memory performance in midlife [77]. This supports the work we carry out in the Learning to Live Program, where we have observed how physical activity improves motor and cognitive functions [78, 79]. This can be assessed with the stand-up walk test or by evaluating walking.

Figure 8: Mobility Assessment: Get Up and Go Test. The person sits in a chair with armrests. They are instructed to stand up (start of test and timing), walk 3 meters, and return to the starting chair (end of timing). Interpretation: - < 20 seconds: normal - > 20 seconds: increased risk of falling [2].

Non-Pharmacological Activities

For the past ten years, we have been carrying out a joint program between the Faculty of Medical Sciences of the National University of Córdoba (Extension Secretariat, Institute of Cell Biology, Chair of Cell Biology, Histology and Embryology), the Argentine Diabetes Society (Gerontology Committee), the Argentine Diabetes Federation, the Friends of Diabetics Group Foundation of Villa Carlos Paz, and the United Schools of Integral Taekwon-do. This program focuses on cognitive stimulation, adapted physical activity, social stimulation, support, health education, and metabolic control in older adults with and without diabetes. We have observed a positive effect of non-pharmacological measures on cognitive decline associated with diabetes and other neurodegenerative conditions in older adults [78,79].

Nutrition

The Geriatric Nutritional Risk Index (GNRI) helps us make decisions by assessing nutritional risk through the measurement of current weight, ideal body weight, and serum albumin levels. It categorizes risk according to the GNRI formula value as follows: Major Risk: less than 82, Moderate Risk: 82 to 92, Low Risk: 92 to 98, No Risk: greater than 98.

Formula: GNRI: [1.489 x serum albumin (mg/ml)] + [41.7 x current weight]
Ideal weight

Is related to the prognosis of diabetes mellitus [80], sarcopenia [81], cognitive impairment [82], and depression [83]. Low serum albumin levels are associated with brain atrophy, neuronal damage, and neuroinflammation [84], all mechanisms associated with cognitive decline. Serum albumin is an antioxidant that neutralizes free radicals and reduces damage to nerve cells [85], a key factor in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Oxidative stress also contributes to cognitive and physical decline in frail older adults, and nutritional interventions help mitigate these effects [86]. Low serum albumin levels are associated with a state

of chronic inflammation [87], an important factor in cognitive decline as it promotes the abnormal deposition of amyloid and tau proteins [88]. Weight and ideal body weight are indicators that reflect an older adult's nutritional status. Obesity due to excessive nutrient intake is closely associated with glycolipotoxicity, the development of diabetes mellitus, cognitive decline, and dementia. Unintentional weight loss is a sign of severe decompensation [89]. While older adults lose height, incorporating ideal body weight helps reflect an individual's nutritional status and physical health [90, 91].

Cognitive Stimulation

Within the framework of the "Learning to Live" program, promoted by the Diabetes Friends Group Foundation (FGAD), the Faculty of Medical Sciences of the National University of Córdoba, and the Gerontology Committee of the Argentine Diabetes Society (SAD) [78,79], weekly cognitive stimulation sessions are held with older adults. These one-hour sessions provide a space guided by a psychology professional where exercises designed to challenge and strengthen different social and cognitive aspects are performed. We encourage active participation in mental exercises to maintain and improve cognitive functions, such as memory, attention, language, and executive skills. In addition to the cognitive benefits, these sessions also offer a space to share experiences, concerns, and resources, which promotes a sense of community and support among participants. The importance of these support groups lies in their ability to promote social integration, a sense of belonging, and mental stimulation—fundamental elements for psychological well-being in old age. As Berkman et al. mention, social support and participation in group activities can reduce the risk of depression and improve resilience in older adults. Thus, encounter groups contribute to the emotional health and socialization of older adults [92]. It is crucial to recognize that emotions play a fundamental role in the overall well-being of older adults. According to Baltes and Smith, the proper management of emotions influences adaptation to life changes and the prevention of mental health problems such as depression and anxiety. Therefore, providing these group spaces to share and understand the emotions that arise in the process of aging and cognitive decline improves quality of life [93].

Figure 9: Cognitive Stimulation Workshop.

Adapted Physical Activity

Adapted physical activity based on the practice of Taekwon-do, a martial art, and meditation helps older adults perceive, from the outside, the movements they will perform and, from the inside, sensations, especially the location of each part of their body. This aims to train mobility, balance, coordination, flexibility, strength, muscle and bone mass, orientation, visuospatial memory, attention, and semantic memory by recalling the names of the movements. This takes place within a framework of personalized individual and group stimulation, as participants must coordinate their movements with those of their activity partners and participate in shared events, public presentations, and events such as the "Beto Metrebian National Marathon for People With and Without Diabetes"... [78,79]. We incorporate meditation into these activities as a way to improve self-understanding and enhance self-control and attention.

Figure 10: Taekwon-do orientation exercises for "Older Adults" where they practice spatial orientation

Pharmacological Interventions Aimed at Cognitive Decline

Until recently, no convincing evidence had been found that any specific treatment or treatment strategy for type 2 diabetes could prevent or delay cognitive decline. There would be some benefit to implementing multidimensional treatment, especially indicated for people with functional independence and those in Groups 1 and 2 of the Comprehensive Geriatric Assessment of Older Adults with Diabetes Mellitus [94]. We highlight the importance of metabolic and cardiovascular control, non-pharmacological measures, and caregiver support. We emphasize the importance of pharmacology: Metformin, DPP-4 inhibitors, GLP-1 analogues, and SLGT2 inhibitors [95].

We see how there are drugs to control diabetes that also reduce the risk of cognitive decline [96, 97]. Therefore, we mention the main therapeutic groups, among which we highlight GLP-1 receptor agonists for their neuroprotective actions, especially in cases of obesity and cardiovascular damage, and in cases of severe hypertension, incipient renal failure, and SLGT2.

Biguanides Metformin

Metformin reduced cognitive dysfunction in older adults with diabetes mellitus, always with vitamin B12 monitoring and due to its senolytic action [98]. Zhang QQ et al. and Imfeld et al. demonstrated that metformin reduced the risk of cognitive dysfunction in type 2 diabetes [99]. This would be related to the decrease in cerebral insulin resistance [100], low-grade systemic inflammation, thrombosis [101], control of metabolic syndrome, and reduction of hyperinsulinemia, which can lead to the formation of amyloid plaques in the brain and the onset of cognitive dysfunction [102].

Incretins

Increased activity of dipeptidyl peptidase-4 (DPP4) inhibitors was independently associated with improvement in mild cognitive impairment (MCI) in older adults with type 2 diabetes [103]. By blocking DPP-4, they reduce the degradation of GLP-1, a neurotrophic factor that prevents neurodegeneration, through an effect on neuroplasticity by improving synapse growth and formation [104]. They activate the mTOR pathway and tau hyperphosphorylation, inhibiting hepatic gluconeogenesis, reducing insulin resistance, increasing insulin sensitivity, and inhibiting inflammation [105-107]. Chai S et al., in a meta-analysis based on randomized controlled trials, showed that GLP-1 receptor agonists (GLP-1 RAs) can significantly reduce the risk of stroke in people with established atherosclerotic cardiovascular disease [108]. They demonstrated a favorable effect on cognitive decline in people with type 2 diabetes (T2D) by increasing the activity of brain-derived neurotrophic factor (BDNF), which is decreased by oxidative stress and inflammation. This, in turn, increases neuronal growth and promotes synaptic formation [109, 110]. They appear to reverse amyloid deposition in the cognitive impairment associated with Alzheimer's disease (AD) [111]. However, the Carolina study did not observe a beneficial effect of linagliptin [112].

Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs)

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are antidiabetic drugs with effects on synaptic plasticity, cognition, and cell survival [113]. Semaglutide, a GLP-1 peptide receptor agonist, approved for the treatment of type 2 diabetes and obesity, has shown anti-obesity potential in phase 3 clinical trials such as SUSTAIN and PIONEER. This potential was established in the STEP trials, and preclinical and phase 2 studies indicated the therapeutic potential of semaglutide in non-alcoholic steatohepatitis and neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease, with which diabetic encephalopathy shares pathophysiological and clinical characteristics [114]. It has a modulating effect on addictive behaviors by influencing the activity of the inhibitory neurotransmitter GABA in spontaneous inhibitory postsynaptic currents (sIPSCs) of neurons in the central amygdala (CeA) and infralimbic cortex (ILC), allowing it to act on addictive behaviors such as alcoholism and obesity [115]. It increases neuronal development and plasticity. synaptic activity in the hippocampus of animal models of DM improved cognitive function [116]. They improve chronic neuroinflammation in neurodegenerative diseases: AD, Parkinson's disease (PD), and type 2 DM, and also improve insulin resistance [117].

Selective Inhibitors of Sodium-Glucose Cotransporter 2 (SGLT2)

In preclinical trials, Mone et al. observed that empagliflozin, a selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), reduces vascular damage and cognitive impairment in older adults with DM and heart failure with preserved ejection fraction [118]. This has also been observed in animal models [119].

Dual Glucagon-like Peptide-1 Receptor (GLP-1R) and Glzucagon Receptor (GCGR) Agonists

This group of drugs is particularly indicated in cases of type 2 diabetes mellitus (T2DM) associated with accelerated cognitive decline and obesity, which exacerbates dementia through metabolic dysregulation, neuroinflammation, and disruption of the blood-brain barrier (BBB); however, conventional therapies are not effective. Large-scale, high-quality clinical trials from the REWIND cohort demonstrated that GLP-1R agonists, such as dulaglutide, can reduce the risk of cognitive decline by 14%. Dual/triple agonists (e.g., tirzepatide) show improved glycemic/weight control and synaptic plasticity in animal models, but their neurocognitive mechanisms are still poorly understood. Mazdutide, a dual GLP-1R/GCGR agonist, shows superior weight loss (11-15%) and metabolic benefits in phase III trials. Its neurocognitive effects have not yet been explored. Therefore, there is limited knowledge of how dual GLP-1R/GCGR activation exerts its effects on diabetes-related cognitive impairment (DRI). However, it offers hope in the treatment of cognitive decline associated with diabetes mellitus [120].

Intranasal Insulin (IN)

Insulin receptors in the CNS have a non-metabolic function and act as neuromodulators. Acute or chronic administration of intranasal insulin does not influence blood glucose levels, but it does improve working memory, verbal fluency, attention, and object recognition in animal models, cognitively healthy humans, and people with cognitive impairment. It improves memory by restoring the insulin receptor signaling pathway and attenuating tau protein hyperphosphorylation [121]. Thus, intranasal administration of neuropeptides, such as insulin and orexins, could be a treatment strategy for age-related cognitive decline (ARCD), since dysfunctional neuropeptide signaling is characteristic of ARCD. It is a relatively non-invasive method, directly delivering peptides to the brain. Studies in laboratory animals, young humans, and elderly individuals have shown improvement in cognitive decline after IN insulin administration. Fewer laboratories have evaluated the effects of IN orexins. However, this peptide also shows promise as an effective treatment for ARCD by activating the cholinergic system and/or reducing neuroinflammation [122].

Special Actions: Microbiota, Diabetes, and Cognition

Nutrition is an environmental factor that influences taxonomic changes in the gut microbiota and the development of T2D. Evidence has shown that the effects of nutrition on both parameters are complementary and that changes in the gut microbiota and related metabolites, such as short-chain fatty acids (SCFAs) and branched-chain amino acids (BCAAs), can influence systemic inflammation and signaling pathways that contribute to the pathophysiological processes associated with T2D [123]. We can improve T2D and its complications by remodeling the gut microbiota through interventions such as drugs, probiotics, prebiotics, fecal microbiota transplantation (FMT), and diets [124]. Probiotics and prebiotics such as Lactobacillus rhamnosus LRa05 reduced fasting glucose and insulin resistance by regulating the composition of the gut microbiota in mice with T2D. Polysaccharides derived from Ganoderma lucidum and a high-fiber diet improved insulin resistance and inflammation in mice fed a high-fiber diet (HFD) by reversing gut microbiota dysbiosis and maintaining intestinal barrier integrity, indicating that polysaccharides could be an effective prebiotic for the treatment of diabetes and its complications [125].

Conclusion

We must think, see, and act holistically, recognizing that older adults with diabetes present a complex condition that affects their quality of life. Understanding their categorization according to their functional abilities and the impact of diabetes will allow us to personalize care for older adults with diabetes and cognitive impairment.

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