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REVIEW ARTICLE

Pathophysiological Mechanisms Linking Type 2 Diabetes and Dementia: Review of Evidence from Clinical, Translational and Epidemiological Research

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Abstract: ***Background*:** Type 2 diabetes represents an increasing health burden world-wide and its prevalence in particularly higher in elderly population. Consistent epidemiological evidence suggests an increased risk of dementia associated to type 2 diabetes; the mechanisms underlying these associations, however, remain unclear.

***Objective*:** The study aims to review epidemiological, clinical and pre-clinical data that weigh on pathophysiological links, mechanisms of disease and associations between type 2 diabetes and dementia to identify areas of opportunity for future research.

***Method*:** We searched the following electronic bibliographic databases: PUBMED, EMBASE, SCIELO, MEDLINE and OVID for clinical, translational and epidemiological research literature that summarize diabetes-related risk factors for dementia, metabolic and neurological changes associated to T2D, evidence of therapeutic approaches in type 2 diabetes and its pathophysiological implications for dementia.

***Result*:** Type 2 diabetes mellitus increases risk for all-cause dementia, vascular dementia and Alzheimer's disease. The most evaluated mechanisms linking both disorders in pre-clinical studies include an increase in neuronal insulin resistance, impaired insulin signaling, pro-inflammatory state, mitochondrial dysfunction and vascular damage which increase deposition of β-amyloid, tau proteins and GSK3β, leading to an earlier onset of dementia in individuals with impairment in the glucose metabolism. Neuroimaging and neuropathology evidence linking cerebrovascular lesions, neurodegeneration and particularly small-vessel disease in the onset of dementia is consistent with the increased risk of incident dementia in type 2 diabetes, but consistent evidence of AD-related pathology is scarce. Epidemiological data shows increased risk of dementia related to hypoglycemic episodes, glycemic control, metabolic syndrome, insulin resistance and genetic predisposition, but the evidence is not consistent and statistical analysis might be affected by inconsistent covariate controlling. Therapeutic approaches for T2D have shown inconsistent result in relation to dementia prevention and delay of cognitive decline; lifestyle intervention, particularly physical activity, is a promising alternative to ameliorate the impact of disability and frailty on T2D-related dementia.

***Conclusion*:** Vascular disease, inflammation and impaired brain insulin signaling might occur in T2D and contribute to dementia risk. Evidence from epidemiological studies has not consistently reported associations that could integrate a unified mechanism of disease in humans. Evaluation of the effect of antidiabetic medications and non-pharmacological interventions in dementia prevention in type 2 diabetes is promising but has thus far offered inconsistent results.

Keywords: Type 2 diabetes, diabetes-related dementia, Alzheimer's disease, glycemic control, diabetes complications, dementia.

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1. INTRODUCTION

Type 2 diabetes (T2D) represents an increasing health burden world-wide and its prevalence is particularly high in elderly population. The global trend of ageing is increasing world-wide, especially in the group of elderly people and it is estimated that in 2030, there will be approximately 690 million elderly persons [1]. A review that evaluated the incidence and prevalence of dementia in the recent years concluded that dementia-risk trends are decreasing in some countries over the years, mainly due to improved elderly care [2]. The observed association between dementia and T2D has gathered special attention due to an increasing prevalence and incidence of both dementia and T2D world-wide. Based on epidemiological projections, there is expected to be 552 million of persons with T2D in 2030, most of them in low to middle income countries [3, 4]. Furthermore, there will be an increasing incidence of T2D in developing countries, which is estimated to increase up to 34.0% based on estimations from the Future Elderly Model [5].

Dementia attributable to T2D is relevant due to the increasing prevalence and incidence of both diseases and lack of information about specific pathogenesis of this association [6]. Despite consistent epidemiological evidence, the mechanisms underlying the association of dementia and T2D remain unclear. In this review, we revisit the association of dementia attributable to T2D, with focus on evaluating known risk factors and potential pathophysiological mechanisms in favor and against common disease pathways in both disorders that have been shown in recent studies. We also analyze areas lacking sufficient information in epidemiological, clinical and translational research, which could be helpful for researchers to identify areas of opportunity related to specific pathophysiological mechanisms and risk factors attributable to T2D. Furthermore, we discuss the available evidence on targeted interventions and treatments which could be useful in developing studies focused on preventive schemes for dementia in patients with T2D.

2. METHODS

We searched PUBMED, EMBASE, SCOPUS, MEDLINE and OVID for clinical, translational and epidemiological research literature that summarize diabetes-related risk factors for dementia, metabolic and neurological changes during T2D and the evidence of therapeutic approaches in T2D and its pathophysiological implications for dementia. We reviewed articles which studied diabetes-related risk factors for dementia including risk factors for dementia attributable to T2D, dementia attributable to tight glycemic control, depression in T2D and dementia, and genetic risk factors for dementia in T2D. The review of the metabolic and neurologic changes in T2D and its role in cognitive dysfunction and dementia included: dementia in pre-diabetes and metabolic syndrome, the role for insulin secretion and sensitivity in dementia and T2D, neuroimaging and neuropathology in patients with T2D and its correlation with dementia-related brain changes. Finally, we reviewed the evidence of therapeutic approaches in T2D and its pathophysiological implications for dementia research including the effect of T2D-related medication in dementia risk, medications for cardiovascular risk in T2D and dementia risk and evidence for potential non-pharmacological prevention strategies for dementia in T2D.

3. DIABETES-RELATED RISK FACTORS FOR DEMENTIA

Consistent epidemiological evidence has demonstrated a role of T2D as a risk factor for the development of all-cause dementia. A recent meta-analysis of longitudinal cohort studies concluded that T2D increases the risk of AD in up to 50% (RR 1.5 95%CI 1.2-1.8) and for vascular dementia more than two-fold (RR 2.5 95%CI 2.1-3.0) [7]. Similar results were observed in another meta-analysis, in which the risk for overall dementia associated to T2D increased up to 70% (RR:1.7 95% CI 1.5-1.8), for AD up to 60% (RR 1.6 95%CI 1.4-1.8) and two-fold for vascular dementia (RR 2.2 95%CI 1.7-2.8) [8]. This association also holds true for cognitive function in T2D; indeed, patients with long-standing T2D without diagnosed dementia have lower cognitive function, particularly in attention, working memory and executive functions [3,4,9].

Common risk factors for all-cause dementia in T2D have been studied as secondary outcomes in most studies. Risk factors associated to dementia in T2D include older age, family history of dementia, smoking and comorbidities including hypertension, obesity, dyslipidemia and stroke [11]. Nevertheless, mid-life obesity and hypertension have a paradoxical risk association, given that in later-life, there is evidence suggesting a lower risk of dementia in T2D [12]. Additional risk factors which have not been associated to dementia-risk in T2D, but which have been shown in general population include: sleep disturbances [13], hyperlipidemia and history of depression [14]. Protective factors for dementia shown in general population have also been studied for diabetes, including years of formal education, measured by the grade level attained and/or colleague attendance, occupation and physical activity [15,16]. A systematic review linking variables that contribute to incident all-cause dementia including occupation, lower level of education and socioeconomic status found inconclusive results in patients with T2D [17].

3.1. Risk Factors for Dementia Attributable to T2D

As discussed previously, patients with T2D present an increased risk for all-cause dementia with traditional risk factors for all-cause dementia compared to general population. Indeed, in a retrospective cohort including patients with T2D and dementia, the authors reported that patients with T2D and dementia are shown to be older, more likely female, had higher rates of smoking, longer duration of diabetes and more frequent use of T2D medication [18]. Elderly T2D patients often present with comorbidity, which increases the risk of functional and cognitive impairment; furthermore, a positive correlation between cumulative comorbidities in patients with T2D in relation to dementia risk has been reported. A large prospective cohort conducted in Taiwan reported a higher risk of incident all-cause dementia with increasing number of common comorbidities in elderly individuals with T2D, including hypertension, dyslipidemia, cerebral artery disease, stroke, and kidney disease, adjusted for age [19]. An increase in comorbidities, particularly meta-

bolic disturbances and dyslipidemia have also been linked to increased pro-inflammatory state; T2D has also been linked to chronically increased pro-inflammatory state, with overexpression of cytokines, chemokines and complement proteins, similar to what is seen in post-mortem brains with AD [20]. In mice, chronic inflammatory states have been linked to increased microglial activation [21] and overexpression of tau proteins [22]. This suggests that a pro-inflammatory state as seen in T2D and increased comorbidities may contribute to dementia risk and might mediate these epidemiological observations. Increases in oxidative stress have also been described in AD and has been linked to endothelial dysfunction, which increases the production of reactive oxygen species [23, 24]; a highly oxidative environment, such as what is observed after major cardiovascular events, might interact with amyloid-β (Aβ) plaques and mitochondrial dysfunction to impair tight junction proteins, thus impacting vascular permeability of relevant brain substrates, including insulin [25]. These alterations might interact to increase dementia risk in individuals with high cardiovascular risk, including T2D.

There have been efforts to identify risk factors solely attributable to T2D, including glycemic level and control (26,27,28], years of diabetes exposure [26,29], use of exogenous insulin [30], endogenous hyperinsulinemia [26,31], insulin resistance [32] and hypoglycemia [33] yielding inconclusive results. Research conducted in a large cohort in Ontario, Canada concluded that elderly individuals with recently diagnosed T2D had 12% higher risk in men and 14% higher risk in women for incident all-cause dementia compared to age-matched controls, suggesting that T2D may be considered a risk factor regardless of years of T2D exposure [34]. As will be discussed later, these results lead to the hypothesis that metabolic syndrome and insulin resistance might mediate early stages of dementia and cognitive decline, especially in AD [35,36].

Observational studies have reported an association between insulin secretion and dementia in non-diabetic patients, suggesting that patients with low levels of fasting insulin had higher risk of developing incident dementia, likely attributable to decreased β-cell function [37], nevertheless, a recent meta-analysis showed that rather hyperinsulinemia was correlated with both decreased cognitive function and incident dementia [38]. As commented before, endogenous hyperisulinemia is a predictor of MCI and studies have suggested that insulin variations throughout life may modulate progression of dementia in T2D. A recent hypothesis suggests that alterations in glucose metabolism due to impairment in insulin signaling, inflammation, accumulation of glycation end-products and oxidative stress in the neurons might mediate the progression of dementia [39]. Certainly, the crescent interest in the use of intranasal insulin treatment is a novel area of interest, reporting a good response in functional status and daily activity, but not significantly in cognitive functions [40]. The role of endogenous hyperinsulinemia in subjects with and without T2D and the use of intranasal insulin as a potential dementia treatment are still in progress and may be an area of opportunity for further research.

Whether dementia can currently be considered a T2D complication remains a controversial subject. Pathophysiological correlations between both disorders have been sought out and a potential microvascular component for dementia in T2D has been evaluated in both epidemiological and imaging studies. This was suggested in a longitudinal study performed by Exalto *et al*. where they followed a group of T2D patients and reported that patients with severe diabetic retinal disease are at an increased risk for dementia, reflecting an association with cerebral microvascular disease and incident dementia, even when this is an unknown etiology [41]. Furthermore, impaired renal function also has been shown to be a an independent risk factor for incident dementia, as reported in the TABASCO trial, a prospective cohort that described the association with renal function and brain function using MRI and reported that both conditions increased risk for cognitive decline four-fold as shown by reduced cerebral and hippocampal volume [42]. The Diabetes-Specific Dementia Risk Score (DSDRS), a recent predictive score for evaluation and prediction of incident dementia in T2D developed by Exalto *et al*, considered microvascular complications, including diabetic retinopathy and diabetic kidney disease, and macrovascular complications, including stroke, myocardial infarction and diabetic foot disease, as significant predictors for all-cause incident dementia in elderly patients, suggesting that all risk factors attributable to T2D for incident dementia are accumulative and could be potential targets for intervention [43]. The causal role of microvascular disease has been questioned, especially since neurological changes have been observed in individuals with T2D without evidence of end-organ microvascular damage [44,45]. Disability and functional impairment related to microvascular complications might also be a likely link between T2D-related microvascular complications and dementia, especially since diabetic retinopathy leads to visual impairment, neuropathy to decreased mobility and depression and T2D also leads to sensorineural hearing-loss as a result of microvascular damage [46]. The role of rehabilitation and multidisciplinary interventions to reduce cognitive changes in individuals with disability due to microvascular complications remains to be evaluated as a preventive measure for dementia in these patients with longstanding T2D.

3.2. Hypoglycemia Due to Tight Glycemic Control in T2D and Dementia Risk

Management of glucose levels in the elderly patient with T2D is complex and must consider evaluation of functional and cognitive status to improve glycemic control, long-term functional outcomes and quality of life [47]. Intensive glycemic control in elderly individuals is controversial and has not shown clear cognitive benefits [48], furthermore, regimes based on strict HbA1c goals increased the risk of hypoglycemia, hospitalization and falls, with increased risk of functional impairment [49]. This has led to the suggestion that T2D treatment is often not adequately suited to elderly patients, with many studies suggesting that a large proportion of patients might be overly treated, increasing the risk of hypoglycemia, frailty and dementia [50,51]. Furthermore, a cross-sectional study reported that elderly patients with T2D-related comorbidities including renal insufficiency and cognitive impairments are potentially over treated according to different guidelines [52]. Another retrospective study analyzed risk factors for T2D overtreatment and reported that

individuals with recent cardiovascular events had an increased risk of developing hypoglycemic events [53]. Furthermore, hypoglycemia risk is exacerbated with the use of exogenous insulin and sulfonylureas, especially in patients with chronic kidney disease [54].

There is evidence that supports the hypothesis that hypoglycemic events may contribute to a worsening of the clinical course of dementia and that the risk for incident dementia is exacerbated with each additional episode of hypoglycemia. This was established in a large 27-year follow-up cohort, where authors concluded that in elderly patients with long-standing T2D, cumulative number hypoglycemia increases proportionally the risk for incident dementia [55]. Additionally, an MRI-based analysis of the Atherosclerosis Risk in Communities (ARIC) cohort study showed that patients with hypoglycemia had smaller total brain volume and cognitive decline over 15 years; however, this evidence was not replicated in the ACCORD-MIND MRI trial, where hypoglycemia was not linked to decreased brain volume and abnormal white matter volume [56,57]. Nevertheless, both studies showed poorer cognitive outcomes and a higher rate of cognitive decline in patients with symptomatic hypoglycemia requiring medical assistance. This had led to question whether there is a need of de-intensifying treatment goals in patients with dementia and T2D or those with T2D at increased risk of dementia with specific use of medication that does not contribute to increased risk of hypoglycemic events. Furthermore, a study suggested that a good maintenance of glycemic control may reduce the risk cognitive decline, especially in those with long-standing diabetes, more than a specific goal of treatment [58], reinforcing the idea that specific treatment guidelines must be developed for the treatment of T2D in elderly patients with dementia, MCI or at risk of cognitive decline and dementia.

3.3. Depression in T2D and Dementia

Another condition related to an increased risk for incident dementia is depression. The relation between depression and T2D appears to be bidirectional. Evidence suggests that in patients with depression, there is 60% higher risk of developing incident T2D. This association is attributable to unhealthy behaviors and physiological changes that induce high body stress [59]. This results in dysfunction of the hypothalamic-pituitary-adrenal axis, sleep disturbances and a pro-inflammatory state which leads to impairments in the glucose metabolism [60]. On the other hand, a meta-analysis report that patients with T2D are up to 25% higher risk of developing depression [59]; this risk is even higher in patients using exogenous insulin and in those with T2D complications, particularly nephropathy, neuropathy and sexual dysfunction [61]. This bidirectional association has been linked to worsening course of T2D, and aggravated severity across the range of complications in T2D. The link between T2D, depression and dementia has been explored. Evidence suggest that in patients with depression and T2D there is two-fold higher risk of incident dementia compared with T2D patients without depression [40,41]. In a nation-wide prospective cohort study including subjects with depression and T2D, subjects with both conditions had two-fold higher risk for incident dementia, suggesting a role for depression as an independent risk factor [62, 63]. Conversely, cognitive dysfunction and depressive symptoms could interact and impact adherence of T2D treatment and thus affect glycemic control in T2D patient [64] which can deteriorate glycemic control and lead to more intensive treatment strategies which could impair functional and cognitive status, thus increasing dementia risk in T2D [52,65].

3.4. Genetic Risk Factors for Dementia in T2D

Genetic risk for dementia has become a relevant area of research with potential implications in dementia prevention. Risk variants in the APOE4 gene, specifically with the APOEε4 allele, have been associated to an increased risk of all-cause dementia in most populations [9,66,67]. The APOEε4 gene causes morphologic changes in neuron architecture in patients with dementia, a trait that may be exacerbated in patients with T2D. The association between the APOEε4 gene and T2D was first reported in the Honolulu Heart Program, where subjects with T2D and carriers of the APOEε4 gene had a 3-fold higher risk of developing hippocampal neuritic plaques (95%CI 1.2-7.3), a 3.5 fold-risk of accumulating neurofibrillary tangles in the cerebral cortex (95%CI: 1.2-7.3) and 2.5 fold-risk to develop the same structures in the hippocampus, specifically in AD (95%CI 1.5-3.7) [68,69]. The APOEe4 has been reported to be a frequent variant in some populations [70–72]. Although there is no clear mechanism that completely explains why this allele increases the risk of AD, there are hypothesis proposing a reduction in Aβ-plaque clearance, which increases inflammation and leads to intensification of neurodegeneration. A recent review suggested that currently it is unknown whether the presence of this allele confers an accumulation of misfolded AD-related proteins or if there is a loss of protective mechanisms attributable to this gene [73,74]. Furthermore, APOEε4 allele has been detected in amyloid plaques [75], and may cause mitochondrial disruption and neuronal damage *via* its receptors [76]; the risk allele has also been implicated to promote tau phosphorylation in animal models [77].

Another recently discovered variant which increases risk of incident dementia in T2D is the HHEX_23 AA genotype, which represents the first novel association observed for T2D patients. The HHEX_23 gene codifies for the insulin degrading enzyme (IDE), which can contribute to the pathogenesis of AD and whose alterations have been linked to neurological and cognitive changes in both human and animal models [78]. One study performed in Scandinavian population reported an increased risk of incident dementia in carrier patients of the AA variant in HHEX_23 and observed a significant interaction with the presence of T2D, increasing substantially the risk of incident dementia and AD. In the same study, carriers of the variant presented significant reductions in hippocampal, and gray and white matter observed in MRI imaging. Further studies need to establish the complete role of IDE in AD tissues, and the role of the HHEX_23 genotype in different populations. Genome-wide association studies that evaluate association of genetic variants with dementia risk in individuals with T2D are required to evaluate contribution of ethnic-specific variants in relation to cognitive and pathologic changes linked to dementia, with attention to specific etiologies subtypes of dementia. Evaluation of genetic risk factors for T2D and its implications in

future dementia risk must also be explored in future studies, with attention to preventive strategies in at-risk groups to reduce T2D incidence or the influence of lifestyle changes in the modification of future dementia risk. Functional evaluations in *in vivo* animal models must also be conducted to identify the pathogenic role of such variants and its potential clinical implications.

The identification of specific risk factors for incident dementia in T2D are complex, mainly due to the intrinsic methodological limitations of most studies. First, many of the studies have different main outcomes, with most primarily evaluating the association between dementia and diabetes and risk factor evaluation mostly relegated to secondary analyses which can present biases due to limited power, variable selection and inconsistent definitions and reporting. Second, many of these studies have different methods to define dementia, which might impact patient selection, affect epidemiological estimations of dementia and affect observed associations with potential risk and protective factors. Third, there is a need of longitudinal cohort studies to assess the interaction of traditional risk factors and T2D attributable risk factors, which is an area, lacking sufficient information. Development of future studies to evaluate risk factors for dementia in T2D should focus on follow-up of T2D subjects with known baseline characteristics, consistent definitions and sufficient time to determine disease onset and etiology. Fig. (**1**) resumes the role of risk factors, both traditional and T2D-specific, in modifying dementia risk and leading to clinical and pathologic features of dementia.

4. METABOLIC AND NEUROLOGIC CHANGES IN T2D AND ITS ROLE IN COGNITIVE DYSFUNCTION AND DEMENTIA

4.1. Dementia in Pre-diabetes and Metabolic Syndrome

Evidence from animal and cell models have unveiled common underlying mechanisms linking dementia and T2D, including impairments in insulin signaling and transport, pro-inflammatory state, oxidative stress, mitochondrial dysfunction, advanced glycation end-products, total cholesterol and the APOEe4 allele. As discussed before, there is evidence which suggests that dementia risk attributable to T2D starts to develop as early as pre-diabetic stages and even in the metabolic syndrome, a relation which has been consistently proven. Compared with matched controls, patients with metabolic syndrome and impaired glucose tolerance have reduced cognitive function [79]. Additionally, certain types of clinical and pathological features of dementia appear earlier in individuals with impaired glucose metabolism, which indicates that there may be a prodromal stage linked to insulin resistant or hyperglycemic stages that is present before the onset of dementia. This was suggested in a prospective evaluation performed in the Framingham Heart Study third generation, which assessed dementia-free subjects and demonstrated impaired memory, visual perception and attention performance in individuals with impaired fasting glucose. MRI evaluation showed decreased total brain and occipital lobar gray matter volumes, suggesting structural brain changes which had previously been related to dementia in patients with impaired glucose metabolism [80]. Another retrospective study conducted in Singapore reported that the presence of metabolic syndrome increases risk MCI

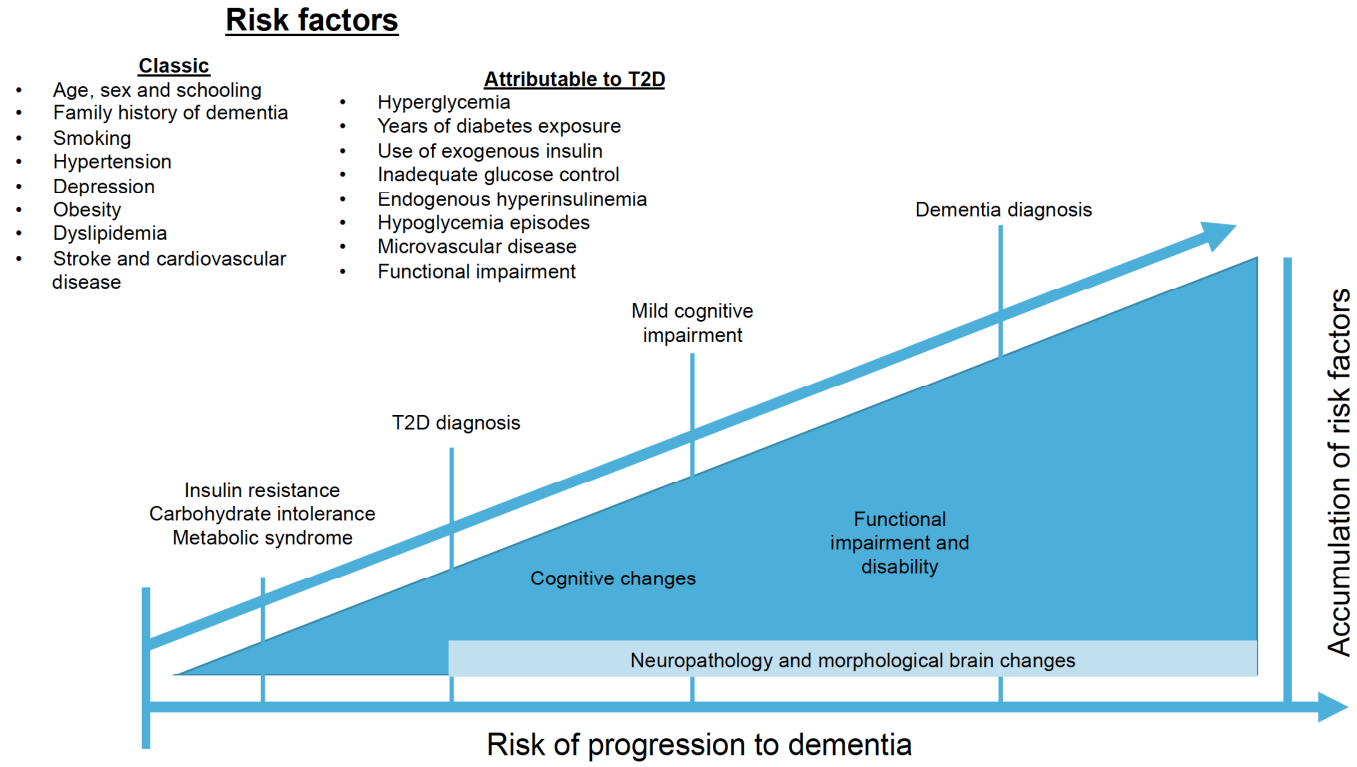

Fig. (1). Cumulative effect of risk factors for dementia in type 2 diabetes (T2D). Evidence suggests that risk factors for dementia in T2D might be classic or attributable to T2D and are cumulative across different metabolic states in interaction with dynamic cognitive and functional changes which increases the risk of cognitive impairment and progression to dementia.

four-fold with a higher risk of progression to dementia compared with controls [81]. This may suggest that cognitive changes may begin prior to T2D onset and are exacerbated with the presence of T2D [82].

Accumulated evidence suggests that the interaction of hyperglycemia and hyperinsulinemia is accumulative across different metabolic stages and is sharply exacerbated in patients with T2D in an age-dependent manner. However, longitudinal studies including elderly populations have suggested that poor glycemic control in patients with T2D contributes to accelerate cognitive dysfunction independently of age [83, 84]. Similarly, young patients with metabolic syndrome have lower cognitive performance and impaired brain structural integrity compared with matched controls, suggesting that metabolic alterations have neurological impacts regardless of age [85]. The interaction of metabolic alterations and age regarding its impact on cognition and brain architecture remain as an attractive area of opportunity for research. Longitudinal studies which evaluate cognitive changes, modifications in brain structure and incident dementia from impaired glucose tolerance through the development of T2D may clarify the clinical course of cognitive dysfunction related to impaired glucose metabolism and tolerance and determine its impact in future dementia risk.

4.2. A Role for Insulin Secretion and Sensitivity in Dementia and T2D

As mentioned earlier, insulin treatment and endogenous hyperinsulinemia could play a major role in the pathogenesis of cognitive dysfunction and dementia in T2D. It is known that insulin acts as a competitive inhibitor of the enzyme that degrades the Aβ plaque, therefore reducing its clearance and potentially leading to accumulation and deposition of Aβ plaques [86]. There is also a hypothesis linking altered brain insulin and insulin-like growth factor-1 (IGF-1) signaling with dementia, especially AD [87, 88]. This may question that the fluctuation in glucose levels may not be the key factor in incident dementia, but instead a fluctuation in insulin levels. This was evaluated in a prospective study conducted in Sweden, in which the authors reported that patients with lower insulin sensitivity, as evaluated using euglycemic hyperinsulinemic clamp, were shown to have 55% higher risk of vascular dementia and those with lower first-phase insulin response assessed using an oral glucose tolerance test had 32% higher risk of AD, suggesting that impaired β-cell function and decreased peripheral insulin sensitivity increase the risk of dementia independent of T2D status [89].

Insulin also has displayed a significant role in modulating cortical responses and cognitive function. In humans, this was demonstrated in a study that assessed cerebro-cortical activity using magnetoencephalography with two-step euglycemic-hyperinsulinemic clamping in obese patients, which concluded that insulin plays a major role in regulating cerebral metabolism by modulating cerebro-cortical activity. This same effect was observed in obese individuals with insulin resistance and carriers of the insulin receptor substrate (IRS)-1 Gly972Arg polymorphism [90]. Another study which evaluated insulin resistant patients using combined FDG-PET and euglycemic-hyperinsulinaemic clamping showed an increased brain glucose metabolism in insulin-sensitive patients, compared with insulin-resistant patients, especially in those brain areas dedicated to subverting appetite and reward [91]; these observations strengthen the link between insulin signaling in the brain, behavioral and cognitive changes related to whole-body glucose metabolism and insulin sensitivity. Despite the strong experimental evidence, these studies do not clarify the precise mechanisms link insulin resistance to the brain, neither if generalized insulin resistance or organ-specific insulin resistance affect neuronal insulin sensitivity. Hypotheses that may explain this relation suggest that long-standing T2D leads to decreased insulin transport mediated by the blood-brain barrier, which leads to decreased brain insulin signaling [92,93]. Studies performed in rodent models have proposed that impairments in insulin receptor signalin, promotes synthesis of glycogen synthase kinase 3β (GSK3β), increases in production of enzymes involved in Aβ processing (β and γ-secretase) and hyperphosphorylation of tau protein [94]. The impact of GSK3β on cognitive function was demonstrated in a study which evaluated that inhibition of GSK3β with lithium chloride in mice leads to decreased cognitive dysfunction compared to controls [95]. Furthermore, mice which are morbidly obese and glucose intolerant at young ages have shown profound cognitive impairment by 12 months, despite not showing significant increases in Aβ formation, proposing a role for peripheral insulin resistance in modulating dementia risk in T2D. [96].

Along with this evidence, recent studies of intranasal insulin use in patients with cognitive impairment have reported improvement in memory and other cognitive functions and tests, offering empirical evidence for a role of insulin in improving cognition [97–99]. This evidence is paradoxical with epidemiological findings, which have shown that exogenous insulin administration increases dementia risk; arguably, the use of exogenous insulin might increase hypoglycemia risk, which might function as a confounder in these associations [100]. In murine models, acute but not chronic intranasal insulin has been show to improve cognitive function, an effect which is halted in diabetic mice [101,102]. Future studies should evaluate the impact of insulin use in cognition and dementia risk, considering confounders such as treatment adherence, hypoglycemia episodes and glycemic targets adjusted for functional status. The role of intranasal insulin to prevent or delay cognitive dysfunction in T2D calls for the development of longitudinal studies with sufficient follow-up to evaluate relevant cognitive outcomes related to functional status and its effect in quality of life in elderly patients with T2D.

4.3. Neuroimaging and Neuropathology in Patients T2D and Correlation with Dementia-related Brain Changes

The correlation of clinical and epidemiological observations linking cognitive dysfunction, dementia and T2D have not shown consistent results in imaging studies. As mentioned earlier, neuroimaging studies have focused efforts in linking changes in brain architecture, brain atrophy, white matter integrity and vascular pathology in patients with T2D; however, few studies have focused on the impact of such changes in cognitive function, progression of cognitive decline and dementia [103]. As commented before, MRI studies have revealed a correlation between brain atrophy and

cognitive dysfunction in patients with T2D, who show reduced brain volume up to 0.5-2.0% compared with controls, particularly in gray and white matter integrity [104]. There is also an increased number of micro-infarctions in lacunar regions caused by small-vessel disease in patients with T2D, compared with controls; nevertheless, the evidence for micro or macrovascular disease as the sole cause for brain vascular pathology in patients with T2D remains controversial. Considering these observations, most conclusions drawn in relation to the etiology of cognitive dysfunction in imaging studies are limited. Imaging studies evaluating trajectories of T2D patients compared to age-matched healthy controls should help unravel structural differences underlying T2D compared to normal aging and studies correlating these changes to cognitive dysfunctions are required to establish a causal and pathophysiological role for such observations in MCI and dementia. Furthermore, most imaging studies are limited by their cross-sectional design and do not include patients with recently-diagnosed T2D [103,104]. Imaging evidence that support most longitudinal observations in dementia research in T2D remains an area of opportunity for further research.

In AD, the characteristic neuropathological feature is the inclusion of extracellular Aβ plaques in neurons, which consist mainly in aggregated Aβ, which is a 4-kDA peptide derived from a sequential cleavage of the Aβ precursor protein (APP) [105]. In T2D, there is a deposit of Aβ plaques in the β-pancreatic cell, also known as human islet amyloid polypeptide (hIAPP) [106-108]. In mice, hIAPP seems to induce apoptosis in the β-pancreatic cell [108] promoting an impaired glucose tolerance; hyperamylasemia in murine causes deposition of hIAPP deposition in cerebral blood vessel walls, leading to endothelial dysfunction and modulated by the APOEε4 gene [109]. Evidence regarding Aβ-pathology in humans with T2D has not been consistent. Autopsy analyses of the Rush Longitudinal Cohort of Aging reported a negative association between T2D and HbA1c on global AD-associated pathology but reported higher odds of cerebral and subcortical infarction, likely supporting the hypothesis of vascular-mediated pathology in T2D-related dementia risk [110]. Furthermore, autopsy, cerebrospinal fluid and PET studies including T2D subjects have not shown increased extracellular deposits of Aβ or increased intraneuronal aggregates of hyper-phosphorylated tau protein or increased biomarkers of Aβ compared with individuals without T2D [111,112]. Nevertheless, imaging and cerebrospinal fluid evaluations of individuals with T2D from the Alzheimer's Disease Neuroimaging Initiative showed decreased lower bilateral frontal and parietal cortical thickness and increased cerebrospinal fluid total and phosphorylated tau, suggesting an impact of T2D in neurodegeneration independent of AD-related pathology [113]. Overall, no overarching, unifying mechanism has been proposed relating T2D, cognitive dysfunction and dementia based on neuropathological or neuroimaging studies, most likely due to the heterogeneity of evaluated populations, scarcity of long-term evaluations which correlate these findings and inconsistent definitions regarding the differences between diabetes-related cognitive dysfunction, MCI and dementia, which have led to inconclusive observations [100]. Studies focused on precise identifications of T2D-related pathological changes in the brain in individuals with and without MCI and dementia must be conducted to reduce the heterogeneity of available evidence and relate these findings with clinical and imaging observations to propose a unified mechanism for the pathways involved in dementia risk in T2D. Fig. (**2**) resumes available evidence regarding metabolic and neurological changes linking T2D and dementia.

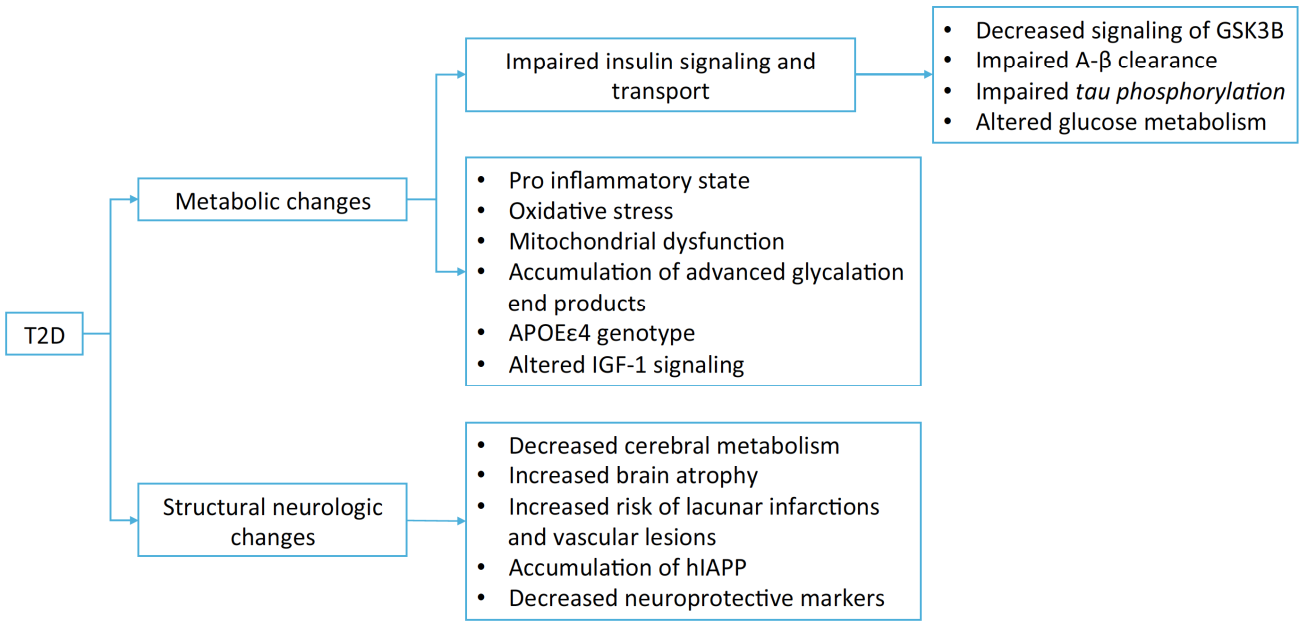

Fig. (2). Changes attributable to T2D in dementia. T2D causes metabolic and morphological changes which are common in dementia. The most recent hypothesis suggest that changes are divided in those that are related to the impaired insulin action, those related to T2D pathophysiology and neurological changes that can be seen in imaging studies.
Abbreviations: T2D: Type 2 diabetes; hIAPP: human islet amyloid polypeptide; GSK3B: glycogen synthase kinase 3β, IGF-1: Insulin-like growth factor 1.

5. EVIDENCE OF THERAPEUTIC APPROACHES IN T2D AND ITS PATHOPHYSIOLOGICAL IMPLICATIONS FOR DEMENTIA RESEARCH

5.1. Effect of T2D-related Medication in Dementia Risk

The impact of T2D treatment in dementia risk remains controversial. In prospective cohorts, including the ACCORD-MIND study, patients with T2D under intensive glycemic control do not experience improved cognition but have significantly lower decreases in gray matter decline [114]. A systematic review by the Cochrane collaboration suggested that evidence regarding the cognitive effect of antidiabetic medication is inconsistent, with the clearest evidence suggesting no benefit of intensive versus standard glycemic control in elderly subjects [115]. Nevertheless, studies which evaluate the effect of T2D treatment on dementia risk have offered a different picture. The SALSA study, a large prospective cohort conducted in Mexican-American subjects, reported a greater risk of incident dementia and cognitive impairment in patients who were untreated for T2D [116]. Another study performed by the 10/66 Dementia Research Group (DRG) in Mexican population reported that the risk of incident dementia was higher in undiagnosed patients with diabetes, who were untreated at that point [117]. A meta-analysis pooling report related to epidemiological studies suggested a decreased incidence of dementia with the use of insulin sensitizers, particularly metformin and thiazolidinediones (TZDs) [118]. These studies have shown that glycemic control at least in part modifies dementia risk, an observation that has been evaluated regarding different specific medications for T2D.

Metformin, the first-line therapy for T2D management, has been evaluated compared to other hypoglycemic medications in relation to its cognitive effect and impact on dementia risk. Compared to sulfonylureas, metformin leads to decreased dementia risk in elderly patients under 75 years, particularly in those with preserved renal function [119]. Nevertheless, one nested longitudinal case-control study suggested that long-term metformin use was associated with higher risk of AD [120]. Metformin has also been linked to reduced dementia risk in comparison to TZDs [121]. Combination therapy with metformin has been assessed in some studies, in one observational study in Taiwan, investigators reported that the combined use of metformin and sulfonylureas had a decreased risk of incident dementia compared with controls [122]; in contrast sulfonylurea monotherapy has not been reported to have significant reduction of incident dementia, compared with metformin [119]. Pilot data from a randomized placebo-controlled clinical trial showed that metformin was associated with improvements in executive functioning, learning, memory and attention with increased orbitofrontal cerebral blood flow [123]. The positive effects of metformin on dementia-related pathophysiology have been evaluated in pre-clinical studies. Metformin and saxagliptin therapy in D-galactose models of AD have shown reversal of memory impairment, oxidative stress, inflammation and tau hyperphosphorylation secondary to impaired insulin signaling [124]. Metformin activates AMPK-dependent pathways, which decreased Aβ-related mitochondrial dysfunction, upregulated genes linked to neuroprotection and decreased activity of caspase 3/9 activity and cytosolic cytochrome c in human neural stem cells [125]; furthermore, metformin was shown to decrease Aβ-induced apoptosis in a MAPK-JNK-dependent way in hippocampal neurons and reduce effects of amyloid deposition in long-term potentiation in murine models fed with high-fat diet [126,127].

The most consistent observations for reductions of dementia incidence in epidemiological settings related to monotherapy for diabetes have been shown for pioglitazone. An observational study reported 47% lower incidence of dementia in T2D patients using pioglitazone for a 6-year period follow-up [128]. Similar results were obtained in a retrospective cohort in Taiwan, where there was a 50% reduction of incident dementia for high-cumulative dose users of pioglitazone [129]. In pre-clinical studies, TZDs have been shown to inhibit neuroinflammation, reduce Aβ-accumulation and plaque formation by promoting Aβ-clearance, and reducing mitochondrial dysfunction and tau-hyperphosphorylation in mice [130,131]. The use of TZDs in reducing dementia-risk in patients with T2D is still an area of opportunity for research, but numerous potential beneficial results in cognition and dementia-related pathophysiology have been reported in animal experimental models and pilot studies of human subjects, which has led to planning and development of future clinical trials (NCT0193156).

Dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitors and long-acting sulfonylureas are attractive medications which have only begun to be explored in dementia research. DPP-4 inhibitors have shown modest but beneficial effects on cognition in individuals with and without cognitive impairment and AD [132]; in pre-clinical studies, DPP-4 inhibitors have been shown to ameliorate cognitive deficits, decrease Aβ formation and deposition and cytotoxicity through activation of AMP-K dependent pathways, which decreased activation of GSK3β and tau hyperphosphorylation by improving insulin action [133,134]. As discussed previously, research evaluating the role of sulfonylureas in dementia prevention have been limited by the increased risk of hypoglycemia in elderly individuals, especially those with functional impairment; the long-acting sulfonylurea glimepiride has been proposed as an attractive alternative, given its use in elderly individuals and its comparably lower hypoglycemia risk. Evidence form pre-clinical studies have shown a role for glimepiride as an antagonist of acetylcholine esterase, a common pharmacological target for dementia, and that glimepiride treatment downregulates binding of Aβ plaques, thus reducing intracellular cholesterol accumulation and activation of phospholipase A2, leading to decreased neuronal synaptic damage [135,136]. Overall, available evidence regarding the use of antidiabetic drugs to reduce T2D-related dementia risk, dementia prevention or cognitive benefits in human subjects are limited by the scarcity of randomized clinical trials, inconsistent follow-up time and lack of statistical power in observational reports. Ongoing clinical trials must assess the benefits of antidiabetic medications longitudinally and correlate their usefulness against functional status.

5.2. Medications for Cardiovascular Risk in T2D and Dementia Risk

The role of medication routinely administered to T2D patients to modify cardiovascular risk and dementia risk is mostly observational. In Taiwan, a large prospective cohort in patients with T2D who were using angiotensin-converting-enzyme inhibitor (ACEI) and/or angiotensin II receptor blockers (ARBs) found that both drugs decrease the incidence of vascular dementia, but not AD [137]. This is explained partly because higher blood pressure levels lead to progression to atherosclerosis and hypoxia, which induces brain damage [138]. Another hypothesis is an increased activation in the renin-angiotensin-aldosterone pathway in T2D, which leads to accelerated progression to dementia [137]; therefore, blockade of this pathway using ACEI/ARB may result in decreasing dementia incidence. Additionally, T2D is associated with impaired autonomic nervous system response, leading to endothelial damage through sustained vasoconstriction, increasing atherosclerosis and formation of atherosclerotic plaque risk, thus decreasing the cerebral blood flow and damaging synaptic connections and neuronal activity in regions involved in cognitive functions including limbic regions, association areas and white matter that links association areas [139]. This effect could be reduced through adequate management of blood pressure and a reduction of sympathetic blood flow, interventions which should be addressed both pharmacologically and increasing physical activity in at-risk individuals. The pathophysiological impact of such interventions remains to be elucidated in future studies.

Although studies have reported that statins are also a protective factor for incident dementia, especially in AD [140], there is evidence suggesting that in general population, statins given at late life do not prevent cognitive decline or dementia [141]. One meta-analysis that included prospective studies which assessed the potential benefit of statins concluded that there is a significant reduction of incident dementia [HR 0.71, 95%CI 0.61-0.82) [142]. The effects of statins in the central nervous system might be explained by the lipid reduction alone; however, a role for the pleiotropic effects of statins, including anti-inflammatory, anti-oxidant, pro-fibrinolytic and anti-proliferative have been proposed as mechanisms to reduce progression to dementia but have not been evaluated in models of diabetes. Furthermore, modifications of cholesterol content in the brain seems to promote a non-amyloidogenic processing pathway at the level of the cell surface, which reduced amyloid accumulation and plaque formation [142]. Another hypothesis is that statins regulate the synthesis of cholesterol end-products like isoprenoids (farnesyl pyrophosphate and geranyl pyrophosphate) which modify the activity of neuronal signaling proteins like RAS and RHO. However, data is still inconclusive and most proposed pathophysiological mechanisms remain a hypothesis [143]. The role of statins in the modification of T2D-related dementia risk is relevant, considering the role of statins in cardiovascular protection in T2D; however, these mechanisms and clinical associations have not been extensively studied and remain as areas of opportunity for future research.

One study performed in Taiwanese subjects reported that daily low mean doses of 40mg of acetylsalicylic acid (Aspirin) reduces de risk of AD-dementia, but not non-AD-dementia, in patients with T2D. Nevertheless, the same report suggested increases in risk of all-cause incident dementia for doses >40mg compared to non-aspirin users [144]. The proposed mechanisms underlying their observations suggest a role for low-dose aspirin in modulating endothelial function and reducing the pro-inflammatory state that has been linked to AD and T2D pathophysiology but an increased risk for vascular dementia and functional impairment with higher doses. These findings are supported by a recent meta-analysis, which suggests that use of non-steroidal anti-inflammatory drugs (NSAIDs), reduces risk of AD in the general population [145]. Further longitudinal data from observational studies including individuals with T2D and the development of randomized, controlled clinical trials are required to assess the role of aspirin and NSAIDs and its adequate dosages in modifying future dementia risk.

5.3. Evidence for Potential Non-pharmacological Prevention Strategies for Dementia in Type 2 Diabetes

Given the recognition of risk and protective factors for dementia that are potentially modifiable, interest has grown in the development of screening methods to identify at-risk patients for the development of studies focused on dementia prevention in T2D. Recently, a novel diabetes-specific risk score for 10-year prediction of incident dementia in 10 years was developed and validated in American population by Exalto *et al*. The score considers variables including age, schooling, depression and T2D-related comorbidities and complications including microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease and acute metabolic events including symptomatic hypoglycemia and hyperglycemic crises. The Diabetes-Specific Dementia Risk (DSDRS) was developed aiming at introducing dementia prediction into daily life clinical practice to detect subjects at high risk of incident dementia [43]. Most of the evaluated factors, as discussed previously, have been linked to increased disability and impaired functional status, both of which increase dementia risk. Future studies should evaluate the role of multidisciplinary interventions in reducing dementia risk by targeting disability, impaired quality of life and functional status related to micro and macrovascular complications of T2D. Evaluating the role of DSDRS in assessing dynamic changes in risk overtime or the development of a dynamic risk score for follow-up would aid in monitoring changes in dementia risk and developing tailored interventions for at-risk individuals.

Since intensive glycemic control has been linked to poorer outcomes in elderly patients with T2D with limited cognitive benefit, a growing interest has emerged in evaluating non-pharmacological interventions, particularly cognitive and metabolic screening, diet and physical activity. One way of detecting patients at high risk of dementia is by detecting MCI [146], this subset of patients have shown a higher risk of developing dementia compared to patients without T2D and MCI [66]. Routine cognitive evaluations should be conducted for T2D patients and studies must be assessed to evaluate the optimum point to intensify screening by focusing on maximizing risk reduction. Views proposed

in other reports also support that preventive measures in the general population, including healthy lifestyle and a favorable cardiovascular risk factor profile, maybe in accordance of reducing the incidence of T2D, which is the better preventive measure to impact its associated dementia risk [147]. The Alzheimer Disease Association concluded in a recent review that there is strong evidence to suggest that regular physical activity, management of cardiovascular risk factors including obesity, smoking and hypertension and healthy lifestyle changes including dietary and cognitive training can delay onset of dementia [15]. Indeed, recent evidence has suggested that physical activity modulates the increases in dementia risk attributable to both of APOEε4 allele and T2D in population that has an increased incidence of T2D, mostly by reducing cardiovascular risk, modulating peripheral insulin sensitivity and improving functional status [148]. Non-pharmacological interventions are promising in modifying long-term dementia risk and are currently an area of opportunity for future research. Table **1** resumes the observed mechanisms for both pharmacological and non-pharmacological interventions in modifying T2D-related dementia risk.

Table 1. Clinical benefits and proposed mechanisms of medications commonly used in T2D on dementia risk.

Medication	Clinical Evidence	Proposed Mechanisms
Metformin	•Decreased dementia risk in patients <75 years, with preserved renal function •Decreased dementia risk in combination with sulfonylureas or pioglitazone •Improves in executive functioning, learning, memory and attention with increased orbitofrontal cerebral blood flow from randomized, controlled, short-term clinical trials	•Activation of AMPK-dependent pathways, decreasing Aβ-related mitochondrial dysfunction, activity of caspase 3/9 activity and cytosolic cytochrome c in human neural stem cells. •MAPK-JNK-dependent decreases in Aβ-induced apoptosis in hippocampal neurons. •Reduction on the effects amyloid deposition in long-term potentiation in mice. •Reversal of memory impairment, oxidative stress, inflammation and tau hyper-phosphorylation in mice.
Pioglitazone	•47% lower incidence of dementia in diabetic patients using pioglitazone for a 6-year period •50% reduction of incident dementia for high dose users.	•Inhibition of neuroinflammation in mice. •Reduction in Aβ-accumulation and plaque formation by promoting Aβ-clearance •Reduction ofmitochondrial dysfunction and tau-hyperphosphorylation
DPP-4 inhibitors	•Modest but beneficial effects on cognition in individuals with and without cognitive impairment and AD.	•Amelioration of cognitive déficits, Aβ formation and deposition and cytotoxicity through activation of AMP-K dependent pathways. •Decreases in activation of glycogen synthase kinase 3β (GSK3β) and tau hyperphosphorylation by improving insulin action.
Sulfonylureas (glimerpiride)	•Not available	•Antagonist of acetylcholine esterase •Downregulates binding of Aβ-plaques, reducing intracellular cholesterol accumulation and activation of phospholipase A2.
ARB/ACEI inhibitors	•ACEI and/or ARB decrease incidence of vascular dementia, but not AD	•Blood pressure control reduces progression of aterosclerosis and hipoxia. •Inactivation of the renin-angiotensin-aldosterone pathway, which has been linked to accelerated progression of cognitive decline. •Alleviation of endotelial dysfunction, leading to improved cerebral blood flow and neuroprotection.
Statins	•Reduction in the incidende of all-cause and AD-dementia.	•Activation of non-amyloidogenic processing pathways at the level of the cell surface, thus reducing plaque formation. •Reduction of cholesterol end-products, improving neuronal signaling. •Anti-inflammatory, anti-oxidant, pro-fibrinolytic and anti-proliferative effects.
Aspirin	•40mg of acetylsalicylic acid (Aspirin) reduces de risk of AD-dementia, but not non-AD-dementia •Increases in risk of all-cause incident dementia for doses >40mg compared to non-aspirin users	•Modulating endothelial function and reducing pro-inflammatory state linked to AD and T2D pathophysiology •Increased risk of bleeding, leading to vascular dementia and functional impairment with higher doses.

Abbreviations: T2D: Type 2 diabetes; AD: Alzheimer's disease, Aβ: Amyloid β, ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers, DPP4: Dipeptidyl peptidase 4 inhibitors.

Table 2. Areas of opportunity for research in T2D-related dementia risk. Conclusions in gaps in knowledge and required studies in diverse areas of opportunity for research in the evaluation of the effect of T2D in cognition and dementia risk. Abbreviations: T2D: Type 2 diabetes; AD: Alzheimer's disease, GWAS: Genome-wide association studies, EWAS: Epigenome-wide association studies.

Research Area	Areas of Opportunity for Research
Pre-clinical	•Experimental designs with increased correlation with observational and clinical findings. •Confirmation of findings from previous studies evaluating impact of biological factors in cognition in models of dementia, AD and T2D. •Effects of antidiabetic effects of medication in *in vivo* models of dementia, AD and T2D. •Systems biology approach to correlate findings with metabolomics, proteomics and gene expression studies.
Observational	•Development of cohort studies aimed at evaluating risk factors for dementia focused in T2D patients, with strong and consistent cognitive outcomes. •Standardization of follow-up time and risk factor evaluation, to ensure statistical power in population-based samples. •Consistent covariate controlling, including traditional risk factors for dementia, use of medication and functional status, along with standardization of analytic techniques for comparison across-studies. •Evaluating the effect of ethnicity, gender and socioeconomic factors in T2D-related cognitive impairment and dementia risk. •Development of GWAS, EWAS and whole-exome sequencing studies aimed at evaluating ethnic-specific variants that increase risk of dementia in T2D, with particular focus on the effetc of known and novel variants attributable to increased T2D risk in susceptible populations
Clinical	•Development of experimental models to confirm findings from pre-clinical studies. •Development of long-term clinical trials evaluating the effect of T2D-related medications in cognitive outcomes in individuals with T2D. •Longitudinal imaging studies paired with metabolic evaluations to assess observations obtained through observational and pre-clinical studies. •Evaluate the direct effect of functional impairment and metacolic changes in cognition in patients with T2D. •Development of specific treatment reccomendations and studies on the effect of deintensification of clycemic control on cognition an dementia risk

CONCLUSION

Here, we resume an overview of pathophysiological links between T2D and dementia reviewing evidence from epidemiological and clinical studies in correlation with data obtained through biological an experimental medicine. A consistent mechanism linking T2D to dementia risk has not been reported in human research and evidence regarding animal models is skewed towards shared mechanisms between AD-dementia and T2D. Current hypothesis have overviewed the role of metabolic disturbances in T2D, including cerebral insulin resistance, accumulation of glycation end products and inflammation, correlated with the effects of T2D and cardiovascular medication on cognition and dementia risk. Epidemiological and clinical studies have also suggested that the clinical course of T2D, including inadequately intensive glycemic control, increasing number or comorbid conditions or T2D-related complications might lead to impaired functional and cognitive status which increase dementia risk. Even though T2D patients are also affected by so-called traditional dementia risk factors, the identification of T2D-specific risk factors in samples powered to evaluate differences with rigorous dementia definitions and consistent confounding control are required for the development of screening methods for future research.

The heterogeneity of the available evidence of T2D-related factors and its role in dementia risk calls for targeted studies aiming at optimization of T2D treatment using a multidisciplinary approach that combines pharmacological and non-pharmacological interventions evaluating its cognitive affect and impact on dementia risk modification, some of these gaps are resumed in Table **2**. Likewise, possible interventions that can decelerate the progression to dementia and cognitive decline must be explored in both observational and experimental settings of individuals with T2D. Despite strong and consistent evidence in biological and experimental medicine, translational studies that evaluate findings from observational studies are required in the pre-clinical setting to study mechanisms of disease and alleviate the intrinsic confounding of most observational settings. Given the increase in T2D prevalence in an aging population, future studies should shed light on these gaps in knowledge and further out understanding in what is becoming an important emerging complication in elderly patients with T2D.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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