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CORRELATIONS BETWEEN COGNITIVE DECLINE, ATRIAL FIBRILLATION AND DIABETES MELLITUS

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Current evidence indicates that the global prevalence of dementia is progressively increasing, largely because of population aging. Nevertheless, age-specific incidence rates of dementia have declined in several regions over recent years, likely reflecting improvements in lifestyle factors and increased attention to health. A growing body of scientific evidence demonstrates that chronic lifetime exposure—beginning as early as young adulthood—to cardiovascular risk factors such as arterial hypertension, diabetes mellitus (DM), obesity, smoking, and sleep disturbances significantly contributes to the development of cognitive decline (CD) and dementia. These risk factors may trigger and amplify diverse neuropathological processes underlying CD, gradually reducing the brain's functional reserve. Consequently, their early identification and effective management are essential to prevent progression toward dementia. Cognitive impairment has been shown to interact with cardiovascular diseases including coronary artery disease, abnormal blood pressure, heart failure, and arrhythmia. Cardiovascular conditions may contribute to CD through mechanisms such as cerebral hypoperfusion, structural brain alterations, inflammation, β-amyloid deposition, and neuroendocrine dysregulation. The coexistence of atrial fibrillation (AF) and type 2 diabetes mellitus (T2DM) may further increase the risk of CD. Understanding these complex interactions and developing effective preventive strategies are of paramount importance in reducing the risk of dementia progression.

Keywords: atrial fibrillation, diabetes mellitus, cognitive decline

INTRODUCTION

The progressive expansion of the global geriatric population, together with the increasing prevalence of cardiovascular risk factors in the general population, has led to a steady increase in the number of individuals affected by dementia[1,2]. Health care systems will be required to make substantial efforts to cope with the associated high costs[3,4].

The prevalence of elderly individuals with multiple age-related degenerative conditions – including cardiovascular disease (CVD), cognitive decline (CD), and dementia – is also steadily rising[3–5]. In older patients with comorbidities, CD frequently remains undiagnosed, further complicating clinical management[3,6].

Lifetime exposure to cardiovascular risk factors significantly increases the likelihood of developing cognitive impairment of varying severity, often progressing to clinically manifest dementia of both vascular and Alzheimer's type[1,2].

COGNITIVE DECLINE (CD)

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, cognitive impairment (CI) is defined as a noticeable decline from a previous level of functioning in one or more key cognitive domains. These include executive function, perceptual–motor function, learning and memory, language,

complex attention, and social cognition[7,8]. CI is characterized by reduced performance in one or more of these areas, such as learning and memory, sustained attention, communication, decision-making, motor or social cognition, and perception[3,9].

CD is among the most disabling conditions worldwide, and health care systems must increasingly address the burden posed by multiple age-related degenerative disorders in the context of rising life expectancy[3,5]. Early detection of cognitive changes is of particular importance, as individuals with CI have an estimated 10% annual risk of progressing to dementia[3].

Aging is one of the most significant risk factors for CI. Advancing age is associated with a decline in nervous system and organ function, as well as with biological changes such as impaired ability of cerebral microvascular endothelial cells to form capillary-like structures, impaired autoregulation of cerebral blood flow, and increased oxidative stress[7,10–12].

The mechanisms underlying CD are multifactorial and remain incompletely understood, although the role of cerebral arterial atherosclerosis is widely recognized[3]. CD is regarded as a precursor to dementia, a major global challenge that alters patients' functional capacity and leads to progressive loss of independence, ultimately requiring support from family or local social care institutions[3,13].

CD encompasses a broad spectrum of severity depending on its impact on patient independence, ranging from mild forms (where individuals can still manage daily activities) to severe CI (where self-care abilities are partially or completely lost)[3,6]. Notably, CI often remains undetected, particularly in older patients with multiple comorbidities[3].

DIABETES MELLITUD TYPE 2 (T2DM)

Type 2 diabetes mellitus (T2DM) represents a major global health concern, as the number of affected individuals continues to rise[4]. T2DM is considered to contribute to the early onset of systemic atherosclerosis[3,14]. In 2017, its global prevalence was estimated at 8.8%, and it has continued to increase annually, making it one of the most common chronic diseases worldwide[3,15]. By 2019, 463 million people (9.3%) were diagnosed with T2DM globally, and this figure is projected to reach 578 million (10.2%) by 2030 and 700 million (10.9%) by 2045[4,16,17].

T2DM primarily affects adults aged 40–59 years in low- and middle-income countries, likely due to the higher prevalence of obesity and insulin resistance (IR) in these regions[4,18]. Importantly, T2DM has been consistently associated with an increased risk of dementia[1,2]. Individuals with T2DM are estimated to have a 1.5-fold higher risk of developing CD and dementia, and more than 45% of diabetic patients present signs of mild CD[4,19].

T2DM is characterized by metabolic dysregulation that leads to multiple complications, including peripheral neuropathy, diabetic nephropathy, and diabetic retinopathy. These complications contribute significantly to the development of CVD and peripheral artery disease (PAD), ultimately resulting in reduced quality of life[4,16,20,21]. Neuronal function also depends on adequate cerebral glucose metabolism, further highlighting the critical link between diabetes and brain health[4,16].

Evidence from clinical studies indicates that patients with T2DM who develop one or more microvascular complications, including neuropathy, retinopathy, or nephropathy, have a markedly higher risk of CVD, heart failure (HF), stroke, and cardiovascular mortality compared to those without such complications[20]. This finding underscores the role of T2DM-induced microvascular damage in exacerbating cardiovascular impairment and further diminishing quality of life.

T2DM may promote the early onset of CD through several mechanisms: (1) the neurodegenerative effects of both hypo- and hyperglycemia; (2) the presence of subclinical or clinical atherosclerosis; and (3) insulin resistance (IR). The latter increases cerebral β-amyloid generation, producing neurodegenerative effects in the brain independently. IR is a key driver in the development of both T2DM and atherosclerosis, playing a central role in the progression of these pathologies[3,18,22]. IR increased oxidative stress, and chronic low-grade inflammation are considered major determinants of CD in patients with T2DM[1,23]. Structural brain alterations, including hippocampal lesions and atrophy, reduced gray matter density, and impaired glucose metabolism, may also contribute to neurocognitive dysfunction in these patients[4,24].

Multiple studies have confirmed a direct association between T2DM, CI and dementia.

Clinically, this association is reflected in impaired verbal fluency, frontal-executive and visuospatial dysfunction, deficits in complex motor abilities, slower processing speed, and reduced attention[4,16,21]. Furthermore, alterations in insulin levels may interfere with β-amyloid (Aβ) degradation, a pathological hallmark of Alzheimer's disease development[4].

A recent meta-analysis of 14 cohort studies including 2.3 million individuals with T2DM, of whom 102,174 had dementia, demonstrated a significantly increased risk of dementia (relative risk [RR] 1.6, 95% CI 1.5–1.8 in women; RR 1.6, 95% CI 1.4–1.8 in men). This analysis also highlighted a direct relationship between the duration and severity of diabetes and dementia risk in this patient population[1,25]. Additional evidence suggests that T2DM may impair neuronal and cognitive function through changes in glucose transporter activity, leading to altered neuronal glucose uptake and metabolism. IR, cerebral hypoperfusion due to cerebrovascular disease, recurrent hypoglycemic episodes, and antidiabetic therapies associated with episodes of hyper- or hypoglycemia may all contribute to neuronal injury[3,26].

A Cochrane review of clinical trials comparing standard versus intensive hypoglycemic regimens (including 11,140 patients with a 5-year follow-up) found no significant effect of intensive treatment on the development of CD (RR 1.0, 95% CI 0.9–1.1) or dementia (RR 1.3, 95% CI 1.9–1.9)[1,2].

Poor glycemic control (HbA1c ≥ 7.0%–7.5%) has also been associated with an increased risk of CD[4,27]. In a Swedish study, Mini-Mental State Examination (MMSE) scores were evaluated in 2,746 patients over the age of 60 across a 9-year follow-up, assessing the effects of T2DM and prediabetes on CD. Brain magnetic resonance imaging performed in 455 participants demonstrated that both prediabetes and T2DM were independently associated with accelerated CD compared to subjects without diabetes ($p < 0.01$). These findings suggest that T2DM and prediabetes may predispose to microvascular damage and accelerated CD[3,28].

It is estimated that more than 45% of diabetic patients present signs of mild CD[4,19,29]. In another recent study including 332 patients with T2DM (mean disease duration 10.17 ± 4.81 years) followed for more than one year, MMSE scores were used to assess the presence of CD. A total of 81 patients (24.4%) were diagnosed with cognitive impairment, with statistically significant MMSE differences observed between patients under and over 60 years of age, as well as in those with longer T2DM duration ($p < 0.001$). The study concluded that CD is common among patients with T2DM, regardless of sex, and correlates directly with both age and disease duration[3,30].

The presence of subclinical or clinically manifest atherosclerosis, as well as the neurodegenerative effects of hypo- and hyperglycemia, promote the early onset of CD[4]. Several studies in the literature have emphasized that individuals with T2DM have lower MMSE scores compared with non-diabetic individuals, and that there is a link between a diagnosis of diabetes established in midlife and the presence of more significant CD[4,31,32].

In another study analyzing 208 patients, including 80 with T2DM and 128 controls, both Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scores were lower in diabetic patients compared with controls ($p < 0.05$). These findings, together with the numerous complications of T2DM, were associated with the development of CD in older diabetic patients[3,33].

The number of people with T2DM continues to rise globally, and projections show that this number will double in the next thirty years, making this condition a major challenge for public health systems worldwide[34].

In a study including 1,519 elderly patients aged ≥75 years diagnosed with T2DM, changes in MMSE scores were analyzed. Participants were divided into groups based on HbA1c levels. The results showed that age, history of cerebrovascular disease, reduced physical activity, HbA1c ≥ 8%, and baseline MMSE score were associated with CD. This study highlighted that in elderly patients with T2DM, an HbA1c value ≥ 8% is an independent factor for CD and is also associated with the severity of CD ($p = 0.029$)[4,31].

In patients with T2DM, the presence of depression may worsen glucose metabolism and HbA1c values, which in turn increases the risk of developing microvascular and/or macrovascular complications, thereby reducing quality of life[4]. In a study evaluating diabetic patients, moderate depression was reported in 8–16% of those with type 1 or type 2 diabetes[4,35]. Furthermore, results showed that compared to non-diabetic individuals, patients with T2DM were two to three times more

likely to be diagnosed with depression[4,36]. Depression impacts patients' psychosocial life and, in those with diabetes, it may be associated with poor glycemic control, leading to reduced adherence to both antidiabetic medication and proper dietary habits, ultimately worsening quality of life[4,37].

ATRIAL FIBRILLATION (AF)

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of 1–3% in the general population and a substantially higher diagnostic probability of approximately 11% in elderly patients[3,38,39]. This arrhythmia is the most frequently documented worldwide, raising constant concerns for health services and having a significant impact on both primary and secondary care[4,6,40]. A diagnosis of AF is associated with up to a 2.4-fold increased risk of developing CD or even dementia[4,41].

The presence of AF in some patients may promote an earlier onset of CD, mainly due to subclinical atherosclerosis in small cerebral arteries. Cognitive impairment may also result from a preexisting proinflammatory state, cerebral microhemorrhages related to long-term anticoagulant therapy, or cerebral hypoperfusion – all mechanisms ultimately leading to brain atrophy[3,42,43].

In certain situations, AF is documented as a diagnosis in patients who experience an acute stroke or in those with silent cerebral infarcts. However, cognitive assessments conducted in recent years have shown that CD can also be observed in patients with AF even in the absence of clinical evidence of stroke[3,44].

The number of patients with AF continues to increase globally, a rise that is linked to the aging of the general population, the growing prevalence of CVD, the presence of multiple associated comorbidities, as well as the broader availability of novel diagnostic methods. Several studies have demonstrated that AF increases the number of hospitalizations due to frequent CVD decompensations, raises the risk of developing chronic heart failure (CHF), and contributes to higher mortality in affected patients[4,6,40].

The role of AF in the development of CD and dementia represents a major societal burden, particularly in elderly patients, where AF is a significant risk factor for stroke. In addition, AF is associated with a higher prevalence of CVD and an increased incidence of overall mortality. The presence of other cardiovascular risk factors – such as T2DM, dyslipidemia, obesity, and impaired renal function – further contributes to the development of CD in these patients, highlighting a multifactorial association with complex pathophysiological mechanisms[3].

As previously mentioned, AF is an important risk factor for the development of CD and dementia. Even in the absence of a documented stroke, numerous recent studies and meta-analyses have confirmed the association between AF, CD, and dementia[4,45]. The results of these studies predict that, over the next four decades, the incidence of AF in the general population will increase by nearly 150%[42,45]. Consequently, in the coming years, the growing number of patients with both AF and dementia will require a substantial increase in healthcare resources and costs[4,42,45].

Several studies have also indicated that the incidence of dementia doubles with every 5.9-year increase in age, suggesting that dementia will affect more than 75 million people worldwide by 2030 and over 135 million by 2050[4,42,45].

The correlation between AF and cognitive dysfunction is complex and multifactorial; therefore, multiple mechanisms have been proposed. Both conditions share several common risk factors, including T2DM, advanced age, obesity, arterial hypertension, sleep apnea, CHF, hyperlipidemia, chronic coronary syndrome (CCS), chronic kidney disease (CKD), physical inactivity, and excessive alcohol consumption[4,45,46].

In addition to ischemic stroke, several mechanisms have been implicated in AF-related CD, including cerebral hypoperfusion, inflammation, brain atrophy, systemic atherosclerosis, associated vascular diseases, and cerebral microbleeds. All these factors may negatively influence the progression toward CD[3,4,42,45,47].

The main factor triggering AF-induced CI is considered to be cerebral infarction[3,42]. However, recent data suggest that AF confers an increased risk of developing early-onset dementia, independent of clinical stroke. Several clinical studies have also described other important mechanisms contributing to the higher risk of dementia and CD in patients with AF, such as silent cerebral infarcts (SCI) and cerebral microvascular disease[3,4,42,45]. Multiple studies have shown that SCI is associated with future clinical

stroke and dementia[4,42]. A meta-analysis reported that AF is associated with a 2.6-fold increased risk of SCI[4,42,48].

In a study including 6,514 participants without dementia, it was shown that, in younger participants, new-onset dementia was strongly associated with the duration of AF[49]. Another study demonstrated that patients with persistent AF had more pronounced cerebral hypoperfusion compared to those with paroxysmal AF or in sinus rhythm[50]. Findings from the Atherosclerosis Risk in Communities (ARIC) study further indicated that persistent, but not paroxysmal AF, was associated with lower cognitive function[51].

In patients with AF, the identification of specific biomarkers that can predict the development of CD may help in screening strategies and patient management. These biomarkers may also be useful in risk stratification among clinically low-risk patients. However, the clinical applicability of biomarkers requires a balance between predictive accuracy and practicality in daily medical practice[3,52].

A prevalence of approximately 9.5% of AF was reported in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS), which assessed CI in 6,432 participants. In patients with AF, the prevalence of mild cognitive impairment/Alzheimer's disease and vascular dementia was higher compared with those without AF, indicating an increased risk of CD (OR = 1.28; 95% CI: 1.04–1.56) and dementia (OR = 2.5; 95% CI: 1.64–3.10)[3,53]. AF may contribute to transient or chronic cerebral hypoperfusion and, potentially, to CD through alterations in heart rhythm, blood pressure, and cerebral blood flow[3,53].

Recent studies have reported that a history of AF, CCS, and CHF is associated with a 77% increased risk of mild cognitive impairment (MCI)[54]. The growing number of elderly patients suffering from AF also has an important impact on CD, with a significant effect on quality of life[4,55]. The negative impact of CVD on cognition may be explained by disruption of the blood–brain barrier or by reduced cerebral blood flow and oxygen delivery, which can result in neurological injury such as cerebral infarctions and an increased accumulation of white matter lesions[4,56,57].

AF is frequently associated with a higher prevalence of cerebral microangiopathy, which may serve as a marker of cognitive changes. Cerebral hypoperfusion and microembolization related to AF may induce ischemic demyelination, similar to that observed in small vessel disease, thereby promoting CD[4,58]. In the ARIC study, with a follow-up of 20 years, 2,106 participants developed AF and 1,157 developed dementia. Greater CD was observed in participants with AF compared to those without AF[4,51].

In a study evaluating patients with AF using Holter monitoring, those with heart rates (HR) below 50 beats per minute and those with HR above 90 beats per minute had a sevenfold higher risk of developing dementia compared with patients with moderate HR. These very high or very low HR contribute to cerebral hypoperfusion[4,59].

Another study assessing CD and subclinical atherosclerosis in 155 patients with systemic hypertension (SH), of whom 84 also had AF, demonstrated that MMSE, Montreal Cognitive Assessment (MoCA), and left ventricular ejection fraction (LVEF) scores were significantly lower, while Geriatric Depression Scale (GDS-15) and intima-media thickness (IMT) values were significantly higher in patients with SH and AF compared to those without AF ($p < 0.05$). In patients with AF, CHA2DS2-VASc scores > 3, and age over 65 years, MMSE scores were significantly lower and IMT significantly higher ($p < 0.05$). This study highlighted that CI is present in hypertensive patients with AF, indicating a direct relationship between CD, AF, age, depression, SH, IMT, CHA2DS2-VASc scores, and LVEF. These assessments are therefore recommended for the prevention of CD in this patient population[60].

In another study including 4,593 patients with AF at baseline, the risk of MCI was approximately 3.43-fold higher in women and 1.73-fold higher in men. In this study as well, dementia risk was elevated in patients with AF. After a follow-up period of more than 4 years, about 30% of the total patients progressed from normal cognitive function to MCI, and 21% developed dementia. Female patients with AF had a significantly higher risk of unfavorable progression (RR = 1.21; [1.04, 1.40]) compared with those without AF, and AF was statistically associated with an increased risk of developing MCI or even vascular dementia[61].

CORRELATIONS BETWEEN TYPE 2 DIABETES MELLITUS (T2DM) AND ATRIAL FIBRILLATION (AF)

In recent decades, due to the increasing global prevalence of both T2DM and (AF), these diagnoses are frequently encountered in the general population, most often coexisting in the same patient[3]. Although it is well established that T2DM and AF are independent risk factors for the development of CD, only a few studies have investigated the consequences of their coexistence[3].

A widely debated topic in the medical literature is the impact of CVD and T2DM in individuals with a very high cardiovascular risk profile, assessed using the Systematic Coronary Risk Evaluation (SCORE2). These conditions can trigger and amplify various neuropathological mechanisms and, consequently, initiate the development of CD by progressively reducing the brain's functional reserve[4].

However, as shown in several studies, other important factors also favor this process, including socioeconomic status, as well as compliance and adherence to therapeutic regimens – both in patients with T2DM and in those with AF. These factors significantly alter mental health status and affect the quality of life of these patients[4,62–64].

Several predictors of low treatment adherence have been identified, including age < 50 years or >80 years, low socioeconomic status, high medication costs, unemployment, personal beliefs regarding drug effects, lack of information and medical knowledge about the underlying disease and necessary treatments, healthcare system limitations, insufficient patient motivation to implement behavioral changes, and various logistical and social barriers[4,62–64].

To assist clinicians in daily practice, an updated SCORE model, known as SCORE2, was developed to improve the 10-year prediction of CVD risk in European populations[65]. SCORE2 provides a more accurate estimation of the impact of CVD and other risk factors on the incidence of both fatal and non-fatal CVD events across different patient categories, such as older individuals and those with DM-2[66]. SCORE2-OP is the most recent cardiovascular risk score and is important for estimating the risk of CVD in individuals over 70 years of age across four geographic risk regions[65].

In a study evaluating 248 patients with very high cardiovascular risk according to SCORE2, of whom 184 had DM-2 and/or AF, and 64 were age-matched controls (without DM-2/AF), patients with AF and those with both DM-2 and AF had significantly lower MMSE scores compared to the non-diabetic control group ($p < 0.05$) (OR = 1.55, 95% CI: 1.13–2.12, $p = 0.007$)[4]. Heart rate (HR) was also significantly higher in the DM-2 and AF groups compared to the control group without AF/DM-2 ($p < 0.05$)[4]. Moreover, SCORE2 values as well as parameters characterizing CD and dementia, depression, and quality of life were more impaired in patients with DM-2 and/or AF compared to those without these conditions[4].

Another study evaluating 160 patients, of whom 50 had T2DM, 54 had both T2DM and AF, and 56 were without T2DM, found that parameters assessing cognitive function (MMSE, MoCA), daily living activities (ADL, IADL), as well as depressive symptoms (GDS-15), were significantly impaired in patients with T2DM and AF compared with those without these conditions. In patients with T2DM, dyslipidemia and advanced age were identified as major risk factors for CD. Another important finding was that CD was more frequent in patients with T2DM, particularly when associated with AF, compared with individuals without T2DM and AF. Logistic regression analysis indicated that, in patients with T2DM and AF, each additional year of age was associated with a 7.3% increase in the risk of early-onset CD (MMSE < 27)[3].

A large study including 429,033 participants without a dementia diagnosis, which used the SCORE2 risk algorithm, demonstrated that subjects with higher SCORE2 values had an increased risk of dementia, vascular disease, Alzheimer's disease, and all-cause mortality. The study concluded that SCORE2 results in the European population may be useful in predicting the risk of dementia, vascular disease, Alzheimer's disease, and all-cause mortality. Furthermore, the study highlighted that individuals with higher SCORE2 scores had an increased risk of developing dementia[4,67].

Further in-depth research is necessary to better understand the factors contributing to the development of CD in patients with T2DM and AF, as well as the potential pathophysiological mechanisms underlying this association. These insights would be valuable for developing more effective strategies for managing T2DM and AF, in

order to prevent the onset of CD and its progression to dementia in these patients[3].

Given the aging global population and the increasing prevalence of T2DM and AF, CD related to these conditions is expected to have a significant impact on healthcare systems worldwide. Therefore, early and comprehensive assessment of patients with CVD, particularly those with AF and T2DM, should be performed to enable timely diagnosis of CD and dementia, while also raising healthcare providers' awareness about the need for tailored therapeutic and psychological management strategies[3].

Currently, various methods are available for the early diagnosis and monitoring of CD, as both CD and subsequent dementia exert a major global impact, both clinically and socioeconomically[1,3].

A complete multidisciplinary approach is recommended, involving specialists in neurology, psychology, psychiatry, and cardiology, with comprehensive evaluation using neuropsychological testing to identify the early onset of CD and attempt to slow progression toward dementia. Furthermore, since in patients with T2DM and AF, any increase in depressive symptoms may aggravate CD and dementia – negatively impacting their quality of life – it is crucial to adequately address depressive symptoms in order to slow CD progression[4].

CONCLUSIONS

AF, T2DM, and CD are major public health concerns, and the number of patients diagnosed with these conditions is expected to grow exponentially in the general population in the coming years. The association between early-life exposure to various cardiovascular risk factors and the later development, in older age, of a variable degree of CD up to clinically manifest dementia – both vascular and Alzheimer's type – is supported by epidemiological and pathophysiological evidence from several specific studies. The progressive aging of the population further increases the proportion of individuals at higher risk of developing dementia.

Prevention currently remains the most effective and truly successful strategy against dementia. Considering the significant clinical and socioeconomic impact of dementia worldwide, achieving optimal control of overall cardiovascular risk in all patients represents an efficient measure to improve the quality of life of individuals with cardiovascular risk factors.

Patients with T2DM and/or AF should be regularly monitored and evaluated to enable the early diagnosis of CD and dementia.

Future studies are required to better analyze the precise mechanisms through which these conditions influence one another, as well as to determine the most appropriate timing for interventions in order to reduce the risk of dementia in these patients.

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