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Alzheimer's disease and Type 2 Diabetes Mellitus: Similar Memory and Executive Functions Impairments?

Soledad Ballesteros[1]* and Maria Teresa Redondo[2]

[1]*Studies on Aging and Neurodegenerative Diseases Research Group, Department of Basic Psychology II, Universidad Nacional de Educación a Distancia (UNED), Madrid, Spain*
[2]*Consellería de Sanitat, Valencia, Spain*

Abstract

Alzheimer´s disease (AD) accounts for more than half of all the cases of dementia. T2DM is a highly prevalent chronic metabolic condition among older adults, and is considered a risk factor to develop AD and other types of dementia. Currently, the incidence of both, AD and type 2 Diabetes Mellitus (T2DM) is a major public health problem in developed countries. Given the similarities between the metabolic and vascular changes occurring in the brain of diabetic patients and in AD patients, a relevant question is whether a series of main cognitive abilities, including episodic memory, working memory and executive functions are similarly impaired in AD and T2DM patients. Recent research has shown a clear dissociation between implicit and explicit memory. Results have shown intact implicit memory in both clinical groups, similar to that of healthy older adults, and impaired episodic (explicit) memory in both groups of patients, especially in ADs. At the same time, visuospatial and verbal working memory (updating and maintenance of information assessed with n-back tasks) showed significant declines in AD and T2DM but larger in ADs. Executive control assessed with the Wisconsin Card Sorting Test (WCST) showed similar declines in both groups of patients. Neuropsychologists and clinicians need to take into account the decline of long-term episodic memory and executive control processes in T2DM for their negative impact on treatment management. At the same time, the spared implicit memory of AD and T2DM patients could be used to support rehabilitation.

Keywords: Alzheimer´s disease; Executive functions; Implicit memory; Episodic memory; Type 2 Diabetes Mellitus; Wisconsin Card Sorting Test (WCST); Working memory

Introduction

The rapid increase in the number of older adults living in our society is accompanying by an exponential increase in the number of citizens who will suffer cognitive decline and dementia in the next decades. Alzheimer´s disease (AD) is the most common senile dementia. This neurodegenerative disease accounts for more than half of all the cases of dementia [1,2].

T2DM is highly prevalent condition among older adults and has become a major public health concern in many developed countries [3-5]. Several studies have focused in AD and T2DM trying to clarify the interconnections between both diseases in order to put forward prevention actions and more effective treatments. Nowadays, the incidence of both, AD and type 2 Diabetes Mellitus (T2DM) is a major public health problem in Europe, the United States and many developed countries [4]. Diabetes mellitus is a metabolic syndrome related to unhealthy diet habits and lack of exercise. This lifelong disorder is characterized by chronic hiperglycaemia resulting from defects in insulin secretion, insulin action, or both. People with diabetes are at risk of suffering cardiovascular and cerebrovascular disease.

T2DM is considered a risk factor to develop AD and other types of dementia [6,7]. A wealth of studies suggest the shared characteristics between AD and T2DM, including impaired neurogenesis, blood brain barrier dysfunction, inflammation, hyperglycemia, insulin resistance, vascular dysfunction and cognitive deficits [8,9]. The metabolic and vascular changes appearing in diabetic patients are in certain ways similar to those occurring in the brain of ADs [10-12]. T2DM patients have elevated basal cortical levels and problems with the hypothalamic-pituitary-adrenocortical axis (HPA) feedback regulation. The hippocampus is also damaged early in the course of diabetes. AD begins with impaired synaptic function, resulting from the accumulation of amyloid-β (Aβ) peptide and causing early memory impairments [4,10]. The pathogenesis of AD begins with impaired synaptic function, which might result from the accumulation of Aβ peptide causing memory loss, especially in the early stages of AD. On the other hand, insulin resistance in peripheral tissues and organs, coupled with relative insulin deficiency, produces T2DM. At the same time, central insulin resistance and reduced brain insulin levels that might have resulted from T2DM produce the accumulation of Aβ and, as a result, AD. Cerebrovascular inflammation, along with accumulation of Aβ, disrupts synaptic function initiating the AD pathological syndrome [11].

It is worth to reconsider the similarity between AD and T2DM taking into account the possible role the fatty-acid receptor G protein-coupled receptor 40 (GPR40). GPR40 induces Ca^{2+} mobilization to reveal dual effects in the brain for adult neurogenesis and stroke as well as in the pancreas for insulin secretion and T2DM. GPR40 is expressed in neurons of the central nervous system and in β-cells of the pancreas [13,14]. GPR40-deficient β-cells secrete less insulin in response to free fatty acids, suggesting that GPR40 influences insulin segregation. This protein is also related to neurogenesis in the adult primate hippocampus [15,16]. However, as most of the studies on this subject have been conducted in animals, much more research with humans is needed to find out whether GPR40 could help to explain the relations between the

***Corresponding author:** Soledad Ballesteros, Facultad de Psicología, Universidad Nacional de Educación a Distancia, Juan del Rosal, 10 28040, Madrid, Spain, Tel: (34) 913986227; E-mail: mballesteros@psi.uned.es

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brain and pancreas as well as T2DM as a risk factor for AD [14,17]. At the moment, as noted by Yamashima [14] whether and how GPR40 expression in the central nervous system could have functional effects is not well understood but the beneficial (e.g. glucose tolerance, brain-lipid sensing, learning and memory) as well as detrimental (e.g. type 2 diabetes mellitus, stroke, retinopathy) roles of this protein must be considered to explain possible divergent results in further human studies.

Do T2DM and AD Patients Suffer Similar Cognitive Declines?

Given the similarities between the metabolic and vascular changes occurring in the brain of diabetic and AD patients [8-10], a relevant question is whether several main cognitive abilities that are critical for independent living such as episodic memory and executive functions are similarly impaired in these two chronic conditions. Although there are many individual differences, episodic memory deficits appear early in the course of AD [2,18]. Results from several recent studies have shown impaired episodic (explicit, voluntary memory) memory and spared implicit (unconscious, involuntary) memory in both clinical conditions [19-23]. Executive control processes are affected early in the course of AD and other dementias [24,25] as well as in T2DM [21-23,26-28].

Previous studies comparing the cognitive functioning of diabetic patients and cognitively healthy older adults showed conflicting results. While some researchers did not find impairments in T2DM patients compared to normal aging [29], others reported some impairments in attention, executive functions, processing speed, and episodic memory [30]. In view of the conflicting results and the scarcity of studies relating cognitive functioning of AD patients with T2DM patients, Redondo et al. compared the performance of groups of AD patients and patients suffering T2DM in tasks designed to assess episodic (explicit) and implicit (unconscious) memory [22,28], and others designed to assess speed of processing, maintenance and updating in verbal and visuospatial working memory and executive functions in order to compare their performance with that of cognitively healthy older adults [28]. The results showed a clear dissociation between implicit and explicit memory: intact implicit memory in both clinical groups, similar to that of healthy older adults, and impaired episodic (explicit) memory in both clinical groups, especially in AD patients. There was a negative trend in episodic memory from healthy elders to T2DM patients and from them to AD patients [22]. At the same time, despite the good glycemic control of the T2DM patients, visuospatial and verbal working memory (assessed with n-back tasks) showed also significant impairments in AD and T2DM but larger in ADs. Working memory also declined in T2DM but less than in AD patients. Executive control assessed with the Wisconsin Card Sorting Test (WCST) showed similar declines in both groups of patients. These results were in line with previous AD studies [24,31-34] and with other T2DM studies [35-37]. Neuropsychologists use the WCST to assess the integrity of frontal lobe functions and perseveration in the same response is interpreted as a failure of the executive control function. An increase in the number of perseverative errors suggests the shrinking of the prefrontal cortex.

Recent research indicates the existence of a shared pathophysiological link between glycemic variability and AD. So, it seems necessary the routinely screening of cognitive functions (especially, long-term episodic memory and executive control functions) in T2DM patients [17]. Longitudinal studies are necessary to investigate whether episodic memory and working memory functions of the diabetic patients with the pass of time deteriorate as much as those of AD patients.

In sort, T2DM patients despite their good glycemic control showed significant working memory declines but as occurred in episodic memory not as large as those shown by AD patients [17,23]. The executive control of the diabetic patients despite their low glycosylated hemoglobin levels did not differ from that of the AD patients [24,28].

Conclusion

The incidence of AD and T2DM represents a major public health problem in modern societies. The fact that T2DM patients suffer early cognitive deficits similar in certain ways to those suffered by AD patients needs to be taken into account when implementing new prevention and intervention programs especially designed for diabetic elders. On the other hand, more research is needed to better understand the interrelations between these two highly prevalent chronic diseases and the role that factors such as glycemic control and comorbidities play in cognitive functioning. Cognitive dysfunction has not been targeted by current management strategies for T2DM [38]. Neuropsychologists and clinicians need to take into account the decline of long-term episodic memory and executive control processes in T2DM for their negative impact on treatment management. At the same time, the spared implicit memory of AD and T2DM patients could be used to support rehabilitation programs developed to teach them how to manage the disease better.

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