Salud Mental 2013;36:167-175
ISSN: 0185-3325
DOI: 10.17711/SM.0185-3325.2013.020

Cognitive Function in Type 2 Diabetes: A Review

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Update by topics

SUMMARY

The aim of this work is to offer an updated review of the major cognitive difficulties that appear in Type 2 Diabetes Mellitus (T2DM), and its association with factors related to the patient compliance or therapeutic adherence proposed by the Pan American Health Organization (PAHO), for chronic diseases; factors such as: characteristics of patient, of the disease and of treatment.

The review was based on an electronic database search (PubMed, PsycINFO and SpringerLink). The period covered was from January 2000 through December 2011, predominating research from the United States, Canada, Holland, England, Japan, Mexico and Germany.

Most of the reviewed articles identified that factors which have shown to be associated with cognitive functioning in T2DM include: glycemic fluctuations, disease duration and type of pharmacological treatment.

As for the changes that occur in the Central Nervous System (CNS), to date there is no consensus as to whether these changes are purely degenerative, vascular or a combination of both.

In the cognitive aspect, it is reported that T2DM is a risk factor for developing mild cognitive impairment. Also, it is reported that chronicity of this condition associated with hypertension, an inadequate glycemic control, and macrovascular complications increases the odds for vascular dementia to occur.

Most affected cognitive abilities are: verbal and working memory, verbal fluency, attention, mental planning and psychomotor speed. These abilities have been related with frontal, temporal and hippocampal structure functioning, which are also compromised on T2DM.

It is concluded that even though some risk factors of the cognitive deficiencies have been identified on T2DM, it is important to determine how they interact, and to what extent they affect overall cognitive performance, and specific functions in this population.

Key words: Type 2 diabetes mellitus, cognitive function, patient compliance, therapeutic adherence.

RESUMEN

El objetivo de este trabajo es ofrecer una revisión actualizada de las principales dificultades cognoscitivas que se presentan en la Diabetes mellitus tipo 2 (DM2) y su asociación con factores relacionados con la adherencia terapéutica propuestos por la Organización Panamericana de la Salud para las enfermedades crónicas como: las características del paciente, de la enfermedad y del tratamiento.

La revisión se basó en una búsqueda en las bases de datos PubMed, PsycINFO y SpringerLink. Se abarcó el periodo de enero de 2000 hasta diciembre de 2011, y predominaron las investigaciones procedentes de los Estados Unidos de América, Canadá, Holanda, Inglaterra, el Japón, México y Alemania.

En la mayoría de los estudios consultados se identificó que las fluctuaciones glicémicas, la duración de la enfermedad y el tipo de tratamiento farmacológico son los factores que más se han asociado con el funcionamiento cognoscitivo en la DM2.

En cuanto a los cambios que se producen en el Sistema Nervioso Central (SNC), hasta la fecha no hay consenso en cuanto a si estos son exclusivamente degenerativos, vasculares o si son una combinación entre ambos.

En el aspecto cognoscitivo, se ha reportado que la DM2 es un factor de riesgo para desarrollar deterioro cognoscitivo leve y que la cronicidad de esta condición, asociada a hipertensión, a un control glicémico inadecuado y a complicaciones macrovasculares aumenta la posibilidad de desarrollar demencia vascular.

Las habilidades cognoscitivas más referidas como afectadas son memoria verbal y de trabajo, fluidez verbal, atención, planificación mental y velocidad psicomotora, las cuales se han relacionado con el funcionamiento de estructuras frontales, temporales e hipocámpicas, que en la DM2 también se encuentran comprometidas.

Se concluye que a pesar de que se han identificado algunos factores de riesgo de las deficiencias cognoscitivas en la DM2, es importante que se determine cómo interactúan y en qué grado influyen estos factores en el rendimiento cognoscitivo global y en funciones específicas en esta población.

Palabras clave: Diabetes mellitus tipo 2, funcionamiento cognoscitivo, adherencia terapéutica.

Translation of the original version published in spanish in: Salud Mental 2013, Vol. 36 Issue No. 2

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Received: May 6, 2012. Accepted: November 20, 2012.

INTRODUCTION

In accordance with the American Diabetes Association,[1] the diabetes mellitus comprises a group of metabolic diseases of multifactorial and polygenic pathogenia. They are characterized by the chronic presence of hyperglycemia, resulting from defects in insulin secretion and/or action on target organs, which in the long term causes negative impacts on several organs and systems (e.g., eyes, kidneys, heart, circulatory system, and peripheral and autonomic nervous system).

This disease is considered a public health problem worldwide, especially in developing countries. According to the figures referred by the World Health Organization (WHO), nowadays there are globally 346 million persons with diabetes and this figure is expected to double in year 2030.[2]

Diabetes is classified in several groups in accordance with its time of appearance and/or type of treatment -type 1 diabetes (DM1), type 2 diabetes (T2DM), gestational and specific-type diabetes-.[1] In Mexico, according to the Secretariat of Health,[3] T2DM is the most frequent in the adult working-age population, since it includes 90% of cases, being the consequence of the ageing of population and of the adoption of lifestyles harmful for maintaining health (e.g. obesogenic eating habits, sedentary lifestyle and daily exposure to stressful situations).

In order to provide comprehensive alternatives upon health care offered to diabetes population, one of the phenomena that has received a considerable interest from different areas of knowledge is the phenomenon called patient compliance or therapeutic adherence, which within this population is generally deficient, and which according to the Pan American Health Organization (PAHO) is defined as "the extent to which a person's behavior —taking medication, following a diet, and/or executing lifestyle changes—, corresponds with agreed recommendations from a health care provider".[4]

According to said organism this phenomenon is divided into 5 mutually interconnected factors: a) socioeconomic, b) health care team-related, c) disease-related, d) treatment-associated and e) patient's characteristics.

Among such factors that have been associated more frequently with the cognitive function in T2DM are the following: a) the patient's characteristics (e.g. demographic characteristics and mood), b) factors associated with the disease (e.g. fluctuations in glycemic levels, duration, complications and related disorders), and c) factors associated with the pharmacologic treatment (e.g. use of oral agents and/or insulin in isolation or combined).[5-15]

As for the cognitive deficits presented in the T2DM, it has been stated that they are the result of malfunctions of cortical and subcortical structures (e.g., frontal, temporal and hippocampal structures), including mainly lapses of verbal and working memory, verbal fluency, attention, mental planning and psychomotor speed.[16-19]

Below is the description of the main neuroanatomical changes presented in the T2DM, as well as the repercussion that such changes have in the cognitive functioning and its association with the factors related to the patient compliance or therapeutic adherence

.

NEUROANATOMICAL CHANGES IN T2DM

With regard to the state of the nervous system in the T2DM, the neurological difficulties described in greater depth have been those related to alterations in the peripheral and/or autonomic nervous system (e.g., neuropathies). As for the changes in the Central Nervous System (CNS) and functions it regulates, so far there is no consensus as to what brain areas are specifically affected and what factors take part in cognitive changes.

According to Zhao and Halcón,[20] the mechanisms insulin regulates at the brain level (e.g., energetic homeostasis, synaptic plasticity and neuronal survival) are diminished with diabetes, which affects the amyloid beta's metabolism, causing its accumulation in both cortical and subcortical structures (e.g., frontal, temporal and hippocampal structures).

This way, it has been stated that the alterations observed in the CNS of diabetics seem to condition the appearance of a "diabetic encephalopathy", which presents more often in persons who have an improper glycemic control on a chronic basis and also present macrovascular complications.[21]

It bears mention that the evidence of said changes is not conclusive, since it has been referred that they are insidious and are not statistically significant when the T2DM is considered as the only causative factor. That is, taking into account that diabetes normally comes with other disorders considered as cardiovascular risk factors (e.g., hypertriglyceridemia, hypertension, obesity and atherosclerosis), they also can contribute to said changes.[22,23]

Through the use of magnetic resonance imaging it has been identified that there are two alterations associated with the changes presented by the CNS in T2DM (Table 1):

1. *Brain Disease*: The T2DM is expressed by way of white matter lesions and lacunar strokes, generally with an asymptomatic presentation and associated to the chronic exposure of hyperglycemia conditions and to a long-term disease.[17,23]
2. *Neuronal Degeneration*: This degeneration conditions the presence of brain atrophy predominantly on frontal, temporal and hippocampal regions, which in turn is associated with chronic conditions of microalbuminuria, insulin resistance and with the presence of hypertension and macrovascular complications.[16,18,19]

Table 1. Hallazgos de neuroimagen con rendimientos cognoscitivos en la DM2

No.	Authors	Origin	Design	Sample	Technique and/or instrument	Findings
1	Den Heijer et al. (2003).	Netherlands	Longitudinal	41 elderly diabetics 465 controls	* IRM[a] * Lists of words	DM2 is associated with hippocampal and amigdalar atrophy, which is a risk factor to develop DATb.
2	Décary et al. (2005).	Canada	Cross-sectional	30 elderly with chronic diseases 20 controls	* EEG[c] * MMSE[d] * DPRe * Rey's Figure * FFS[f] * Stroop * TMT AB[g]	In chronic diseases deficits in attention and working and differed memory occur, together with a slow frontal activity.
3	Manschot et al. (2006).	Netherlands	Cross-sectional	113 diabetics 51 controls	* IRM[a] * Raven * TMT AB[g] * Stroop * Rey's Figure * DCWAIS-III-R[h]	White matter lesions and cortical atrophy are associated with failures on processing speed and memory.
4	Brands et al. (2007).	Netherlands	Cross-sectional	40 elderly diabetics	* IRM[a] * Raven * Corsi's Cubes * RAVLT[i] * Rey's Figure * TMT AB[g] * CNT[j] * LFT[k]	White matter lesions and cortical atrophy are associated with deficits in viso-construction.
5	Manschot et al. (2007).	Netherlands	Cross-sectional	122 diabetics 56 controls	* IRM[a] * Raven * TMT AB[g] * Stroop * Rey's Figure * DCWAIS-III-R[h]	Slight association between cortical and subcortical atrophy with cognitive performance.
6	Cervantes et al. (2011).	Mexico	Cross-sectional	51 diabetics	* IRM[a] * MMSE[d] * COGNISTAT	Association between dyslipidemia and small vessel disease with failures in attention, construction and analogical reasoning.
7	Hayashi et al. (2011)	Japan	Cross-sectional	61 elderly diabetics 53 controls	* IRM[a] * MMSE[d] * HDS-R[l]	Association between DM2 with hippocampal atrophy.

a=Magnetic Resonance Imaging, b=Dementia Alzheimer's Type, c=Electroencephalogram, d= Mini Mental Status Examination, e=Forward and/or Backward Digit Span, f=Phonological and Semantic Fluency, g=Trail Making Test A and B, h=Digits and Cubes of the Wechsler Adult Intelligence Scale III-R, i=Rey Auditory Verbal Learning Test, j=Category Naming Test, k= Lexical Fluency Task, l=Hasegawa Dementia Scale-Review.

NEUROPSYCHOLOGICAL CHARACTERISTICS OF THE T2DM

Cross-sectional and longitudinal studies have stated that there are important cognitive changes in T2DM compared to non-diabetic populations; such changes are grouped in the following sections:

1. The T2DM may cause the presence of a mild cognitive impairment, especially of amnesic type, which exacerbate due to certain conditions such as superior age and duration of illness, la chronic exposure to inappropriate glycemic levels, microvascular complications and related disorders (e.g., obesity and hypertriglyceridemia).[24-26]
2. It is related to the risk to develop vascular dementia resulting from hemodynamic alterations caused by chronic ischemia and hypoxia, which presentation is more frequent in elderly hypertensive diabetics with macrovascular complications.[26,27]
3. It has been suggested that T2DM is a risk factor that increases the possibility to develop Dementia Alzheimer's type (DAT) in the long term, especially when associated with macrovascular complications and hypertension. Thus, it has been proposed that there might be a combined physiopathologic mechanism between T2DM and DAT.[28,29]

Table 2. Association between Personal Factors and Cognitive Performance in DM2

No.	Autores	Origen	Diseño	Muestra	Instrumento	Hallazgos
1	Arvanitakis et al. (2006).	USA	Cross-sectional	116 elderly diabetics 116 controls	* CERAD[a] * TDB[b] * DS[c] * Stroop	In DM2 deficits in semantic memory and perceptual speed occur, associated with chronic tobacco use.
2	Watari et al. (2006).	USA	Cross-sectional	40 diabetics with and without depression 34 controls	* MMSE[d] * Stroop * TMT AB[e] * DS[c] * CVLT[f] * Rey's Figure * WCST[g] * FF[h] * RFFT[i]	Association of depression and DM2 causes greater deficits of attention, psychomotor speed and executive functioning.
3	Aberle et al. (2008).	Germany	Longitudinal	38 diabetics 421 controls	* NAI[j] * FIWAIS-R[k] * FF[h]	Cognitive changes are restricted to elderly diabetics over the age of 65.
4	Yeung et al. (2009).	Canada	Cross-sectional	41 diabetics 424 controls	* RVLT[l] * TH[m] * AEB[n] * CTT[ñ] * Stroop * DS[c]	DM2 increases the neurobiological effects attributed to age, especially in psychomotor speed and executive functioning.
5	Díaz de León et al. (2010).	Mexico	Longitudinal	8,797 older than 55 years old, belonging to ENASEMo	*Cross-cultural cognitive test	Cognitive functioning is determined by the global health status and is associated with a two-year increas-ed mortality.
6	Zihl et al. (2010).	Germany	Cross-sectional	28 persons with DM1 12 persons with DM2	* TVP[p] * LEWMS-R[q] * Raven	The deficits present in complex tasks, which nature is essential; they cannot be considered as a side effect of depressive symptomatology.

a=Consortium to Establish a Registry For Alzheimer's Disease, b=Boston Naming Test, c=Digit-Symbol, d=Mini Mental Status Examination, e=Trail Making Test Forms A and B, f=California Verbal Learning Test, g=Wisconsin Card Sorting Test, h=Phonological Fluency, i=Ruff Figural Fluency Test, j=Nuremberg Inventory of Old Age, k=Incomplete Figures of the Wechsler Adult Intelligence Scale-R, l=Rivermead Verbal Learning Test, m=Hayling Test, n=Brixton Spatial Anticipation, ñ=Color Trail Test, o=National Study on Health and Aging in Mexico, p=Perceptual Speed Tasks, q=Spatial Localization of the Wechsler Memory Scale-R.

ASSOCIATION OF THE COGNITIVE FUNCTIONING WITH FACTORS RELATED TO PATIENT COMPLIANCE/THERAPEUTIC ADHERENCE

1. Personal Factors

1.1. Mood and Demographic Characteristics

Psychological disorders such as depression and anxiety affect diabetics with greater emphasis and, generally, are associated with practically ineffective adherence behaviors.[5]

It has been said that these disorders are more frequent in T2DM and aggravate —especially depressive states— when combined with conditions of the disease (e.g., long lasting, presence of complications and related disorders), with specific demographic factors (e.g., superior age, low educational level and deficient socioeconomic conditions), with substance use (e.g., alcohol and tobacco) and with a deficient glycemic control.[25,30,31]

With regard to the cognitive performance we know that when the above conditions occur, there is an increased risk of suffering from cognitive impairment, characterized by deficits on tasks of verbal memory, attention, processing speed and executive functioning, besides that at the long term this is associated with a higher mortality rate.[5,30,31]

Conversely, Zihl, Schaaf and Zillmer[32] argue that failures in the cognitive performance of T2DM (specifically in working memory and those tasks that need the use of complex skills) have a primary nature, and while being specific they cannot be explained as a side effect of mood symptomatology.

On the other hand, since most of the reviewed studies included samples made up by elderly people, it is mentioned that age is a constant that affects cognitive deficits in T2DM, especially after the age of 65. Failures in psychomotor speed and executive functioning, the most frequent.[33,34]

In order to consult in greater detail the characteristics of the samples researched and the instruments used in the personal factor group, Table 2 describes such research in chronological order.

2. Factors Related to the Illness

2.1. Fluctuations of Glycemic Levels

In spite that T2DM characterizes by the chronic presence of hyperglycemia, it occasionally may be accompanied by opposite states (hypoglycemia), which, apart from having influence on the evolution of the illness, they also cause changes at a cognitive level. Thus, several researches have been conducted with the purpose of establishing what glycemic level (hyperglycemia or hypoglycemia) affects, to a greater extent, the cognitive development of diabetics.

Therefore, it has been observed that the chronic states of hyperglycemia, besides of favoring the presence of microvascular complications and neuropathies, they also cause toxic biochemical effects that increase the accumulation of residues caused by glycolysis, generating in turn an ischemic brain damage associated with deficits in psychomotor speed and selective attention.[35]

In the same sense, it has been identified that when hyperglycemia presents in a severe way, in figures higher than 300mg/dL, it increases the possibility of presenting greater deficits, especially in working memory tasks.[36]

On the other hand, as for the hypoglycemia states, it has been said that the chronic presence of such state, apart from intensifying the appearance of microvascular complications at the long term, it also affects accuracy at attention tasks.[37]

Regarding the fluctuations caused in the glycemic levels during the neuropsychological evaluation process, it has been pointed out that, when such levels elevate throughout the evaluation (greater than 121 mg/dL), deficits result on psychomotor speed and verbal fluency.[38]

2.2. Duration, Complications and Comorbidity

It has been expressed that cognitive deficits presented in T2DM are the result of the interaction of age, duration and complications of the disease, hence memory (especially verbal memory), psychomotor speed and executive functioning are the more often affected aspects.[10,22,24]

Likewise, it is mentioned that this combination have a negative influence on the physiopathology of the cognitive impairment found in diabetes, since such conditions cause, in general, a greater amount of clinical and subclinical cerebral infarctions, apart from the increase and accumulation of amyloid beta in brain structures that regulate cognitive functioning.[20,23]

Furthermore, it has been referred that when T2DM is associated with other chronic sufferings (e.g., hypertension and hypothyroidism) a slow frontal activity occurs, which is significantly associated with deficiencies in attention and immediate and differed working and verbal memory.[39]

On the other hand, it is affirmed that in persons with T2DM there are "clinical markers" (e.g., hyperinsulinemia, retinopathy and microalbuminuria) that when being identified they act as predictors of cognitive impairment, since they are an indicator of the degenerative and vascular effects produced at the brain level, which in turn are associated with the presence of failures in psychomotor speed and verbal and working memory.[40-43]

In order to consult in greater detail the characteristics of the samples researched and the instruments used in the group of described factors, Table 3 describes such research in chronological order.

3. Factors Related to the Treatment

3.1. Pharmacological Treatment

It has been stated that if hyperglycemia is controlled, and if also the insulin sensitivity is increased or its residual production promoted, then it is possible to reduce adverse effects in the cognitive functioning that are present in T2DM.[14]

In addition, it refers that cognitive impairment is present to a greater extent in those persons whose treatment requires the use of insulin, compared to people who use oral agents or control their disease through a diet and physical activity.[13,35]

Nevertheless, it is important to emphasize that since pharmacological treatment scheme for persons with T2DM is staggered and the disease evolution should be considered, possibly cognitive impairment is the result of the combination of duration, complications and comorbidity of the illness, and not only the result of the type of the prescribed pharmacological treatment.

Moreover, regarding the time required to detect changes on the cognitive development, Shorr et al.14 observed that the monotherapy with oral agents administered during 24 weeks considerably improved such development, except for working memory tasks, since the deficits continued.

3.2. Following a Diet

Undoubtedly, the habit of following a proper diet affects positively on any individual's general health, and for diabetics, this is an essential condition for treating this disease.

Thus, when it comes to the carbohydrate intake influence on the cognitive development of these persons, some deficits have been found on short-term memory tasks, especially after 30 minutes of eating such food, which probably is associated with the effects produced on the hippocampus and the medial temporal lobe.[44]

Furthermore, Papanikolaou et al.[45] identified that the intake of low-calorie food facilitates cognitive development (verbal and working memory and sustained attention), which is not the case with high-calorie food, since —besides inducing sudden hyperglycemia states— cause failure in delayed recall tasks.

As for the intake of food rich in fat, chronic consumption (an average of six years) of food high in saturated fats and trans fats, besides raising cholesterol levels, in the long term is associated with deficient cognitive performance, in comparison with food containing monounsaturated fats,

Translation of the original version published in spanish in:
Salud Mental 2013, Vol. 36 Issue No. 2

Table 3. Association between Disease Factors and Cognitive Performance in DM2

No.	Autores	Origen	Diseño	Muestra	Instrumento	Hallazgos
1	Ryan y Gekle (2000).	USA	Cross-sectional	50 diabetics 50 controls	* PA[a] * DS[b] * TMT B[c] * Stroop * RWAIS-III-R[d] * TA[e]	Deficient glycemic control causes failures in psychomotor speed and selective attention.
2	Mc Aulay et al. (2001).	England	Cross-sectional	20 volunteer youths	* TEA[f]	Induced levels of hypoglycemia affect accuracy in attention tasks.
3	Hewer et al. (2003).	Germany	Cross-sectional	53 diabetics 29 controls	* TMT A[c] * FFS[g] * CVLT[h]	Glycemic recovery does not cause improvement on the performance of verbal fluency and verbal memory tasks.
4	Hassing et al. (2004).	USA	Longitudinal	258 elderly diabetics with HASi	* MMSE[i]	Association of DM2 and HASi cause higher cognitive deficits, especially after two years.
5	Munshi et al. (2006).	USA	Cross-sectional	60 elderly diabetics	* MMSE[i] * Clock Test	Inappropriate glycemic control causes deficits in high-level cognitive functions affecting self-care behaviors.
6	Suzuki et al. (2006).	Japón	Transversal	13 elderly diabetics	* ADAS-COG[k] * DS[b] * Stroop	Hyperinsulinemia is a biological marker of deficient cognitive performances.
7	Xu et al. (2007).	Sweden	Longitudinal	1173 diabetics	* MMSE[i]	Association of DM2 and hypertension increases the risk to suffer DVI and DATm.
8	Galanina et al. (2008).	USA	Cross-sectional	54 male diabetics	* MMSE[i] * COWA[n]	When glycemic levels (higher than 121mg/dL) elevate, deficits generate in psychomotor speed and verbal fluency.
9	Iype et al. (2009).	India	Cross-sectional	71 diabetics	* TMT A[c] * CERAD[ñ] * RUDAS[o]	There is no association between the illness characteristics with global cognitive performance.
10	Ishizawa et al. (2010).	Japan	Cross-sectional	27 male diabetics with and without overweight 27 controls	* Go-NoGo Tasks * WCST[p]	Impulsive responses are greater in newly diagnosed patients, which is associated with high levels of HbA-1cq.
11	Shimada et al. (2010).	Japan	Cross-sectional	103 elderly diabetics with and without DCLr and with dementia	* MMSE[i] * RVLT[s]	Cognitive deficits are associated with inappropriate HbA1c figures.
12	Grober et al. (2011).	USA	Cross-sectional	104 elderly diabetics	* FCSRT[t] * Regression Series	Inappropriate glycemic control is associated with memory and executive functioning deficits.

a=Pares Asociados, b=Dígito-Símbolo, c=Trail Making Test A y/o B, d=Rompecabezas de la Wechsler Adult Intelligence III-R, e=Tablero Acanalado, f=Test of a=Associated Pairs, b=Digit-Symbol, c=Trail Making Test A and/or B, d=Puzzle of the Wechsler Adult Intelligence III-R, e=Channel Board, f=Test of Every day Attention, g=Phonological and Semantic Fluency, h=California Verbal Learning Test, i=Systemic Arterial Hypertension, j= Mini Mental Status Examination, k=Alzheimer's Disease Assessment Scale (ADAS-COG), l=Vascular Dementia, m=Dementia Alzheimer's Type, n=Controlled Oral Word Association (COWA) Test, ñ=Consortium to Establish a Registry for Alzheimer's Disease, o=Rowland Universal Dementia Assessment Scale, p=Wisconsin Card Sorting Test, q=Glycated Hemoglobin, r=Slight Cognitive Impairment, s=Rivermead Verbal Learning Test, t=Free and Cued Selective Reminding Test.

which do not affect such performance.[46]

On the other hand, it has been pointed out that elderly hypertensive diabetics who have deficient vitamin D long-term levels (during six years) the possibility to present cognitive impairment increases, since the preventive role that this vitamin has in the neurodegeneration is diminished in these persons.[47]

3.3. Physical Activity

Practicing a physical activity everyday for diabetics is one of the priority practices of their comprehensive treatment, since one of the main benefits is the delay of early appearance of this suffering's complications.

There are few studies that have explored the effects that this activity causes in the cognitive functioning. In this

Table 4. Association between Treatment Factors and Cognitive Performance in DM2

No.	Autores	Origen	Diseño	Muestra	Instrumento	Hallazgos
1	Greenwood et al. (2003).	Canada	Cross-sectional	19 diabetics	* MMSE[a] * RVLT[b] * TMT B[c]	Carbohydrate intake in the short term benefits cognitive performance and in the long term generates memory deficits.
2	Rosen et al. (2003).	USA	Cross-sectional	79 male elderly diabetics	* MMSE[a] * TMT AB[c] * Stroop * DS[d] * DPR[e] * TA[f]	There is no specific de cognitive deficit pattern associated with poor adherence.
3	Papanikolaou et al. (2006).	Canada	Cross-sectional	21 diabetics with obesity	* TAVH[g] * TMT AB[c] * DR[e]	High calorie levels cause deficits in verbal and working memory, selective attention and executive functioning.
4	Ryan et al. (2006).	England	Cross-sectional	145 diabetics	* DS[d] * RVLT[b] * CANTAB[h]	Oral agents benefit performance in working memory tasks.
5	Roberts et al. (2008).	USA	Cross-sectional	290 elderly diabetics 1349 controls	* CDRS[i]	Insulin treatment and macro- and microvascular complications are associated with cognitive impairment.
6	Devore et al. (2009).	USA	Longitudinal	1487 elderly female diabetics	* MMSE[a] * EMB[j] * DR[e]	Chronic consumption of saturated and trans fats cause cognitive deficits compared to tconsumption of mono-unsaturated and polyunsaturated fats.
7	Llewellyn et al. (2010).	England	Longitudinal	858 elderly with and without DM2 and HASk	* MMSE[a] * TMT AB[c]	Low levels of vitamin D increase the risk of presenting long-term cognitive impairment.

a=Mini Mental Status Examination, b=Rivermead Verbal Learning Test, c=Trail Making Test A and/or B, d=Digit-Symbol, e=Forward and/or Backward Digit Span, f=Channel Board, g=Hopkins Verbal Learning Test, h=Cambridge Neuropsychological Test Battery, i=Clinical Dementia Rating Scale, j=Boston Memory Scale, k=Systemic Arterial Hypertension.

regard, Brito,[48] through studies conducted on rodents, expresses that the regular practice of this activity induces positive neurobiological changes, since this increases the neural activation and cerebral blood supply in the hippocampus, which is associated with a better performance in spatial memory tasks.

Likewise, it has been related that when diabetics incorporate physical activity into their everyday life, apart from reducing the probability of the appearance of complications common in the disease, they also contribute to the prevention of potential cognitive deficits associated with this disorder.[49]

Moreover, Indelicato[50] emphasizes that, in diabetics, working memory and mental planning are benefited when a physical activity is made on a daily basis, which is also associated with appropriate anthropometric and physiological levels (e.g. body mass index, waist circumference and cardiovascular and pulmonary capacity).

In order to consult in greater detail the characteristics of the samples researched and the instruments used in the group of the treatment factors, Table 4 describes such research in chronological order.

CONCLUSIONS

The physiopathology of the changes of the CNS in T2DM and the relevant cognitive functions that regulate the affected brain structures are attributed to failures on the homeostatic mechanisms that insulin has at a brain level and to the joint presence of disorders considered as cardiovascular risk factors (e.g., hypertension, hypertriglyceridemia, obesity and atherosclerosis).

In spite that there is no agreement, it is suggested that the combined effect of vascular and degenerative damages causes disturbances on the functioning of cortical structures (e.g., front and temporal) and subcortical (e.g., hippocampus), which in turn jeopardizes the cognitive performance of such persons, resulting in a cognitive impairment, expressed in deficits on tasks related to verbal and working memory, verbal fluency, attention, mental planning and psychomotor speed.

According to the review made, it may be affirmed that, depending on the form that the personal, disease and treatment factors combine in diabetics, negative or positive effects will occur on the cognitive functioning of this population.

Translation of the original version published in spanish in: Salud Mental 2013, Vol. 36 Issue No. 2

Thus, the negative effects shall be presented when combined: a) long-term sickness, b) complications and associated disorders, c) inappropriate eating habits, d) lack of exercise, e) mood disorders, f) chronic glycemic control, g) superior age and h) low educational level and chronic substance use (e.g., alcohol and tobacco).

In contrast, when combined: a) the maintenance of an appropriate glycemic control, b) favorable food habits, c) everyday exercise, d) proper mood and e) high educational level, shall generate positive effects that probably favor upkeep of such functioning in the long term.

It bears mention that the findings referred to in each described section are still very controversial, due to the following questions:

1) Research designs in most of the studies are Cross-sectional and use small samples, which clinical and treatment characteristics are heterogeneous.
2) The neuropsychological exploration of the integrity or cognitive impairment on this population is made most of the times through the use of instruments that assess briefly the general cognitive performance (e.g., use of Mini Mental Status Examination).
3) 3) There is no consensus regarding what are the most recommendable instruments to specifically assess the cognitive functions of this suffering. There is no consensus either regarding in what moment of the illness evolution the cognitive performance of a diabetic must be assessed.

In this sense, despite the conduction of cross-sectional studies, it is important that in future researches similar samples are used due to their clinical and treatment characteristics, combined with the use of control groups.

In addition, when exploring the cognitive integrity and its possible relation to personal, disease and treatment factors on this population, besides assessing the general cognitive functioning, it is necessary to use a more complex instrument battery to identify in a more precise manner —and according to the illness's evolution moment— the influence of such factors over specific cognitive functions.

This way, in spite some signs about the association between cognitive performance and factors related to patient compliance or therapeutic adherence in T2DM have been put forward, it is important to establish to what extent each factor contributes, or how they interact to preserve or impair such performance, and in what functions the most significant deficits present.

Translation of the original version published in spanish in: Salud Mental 2013, Vol. 36 Issue No. 2

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2008;31:62-67.
2. Organización Mundial de la Salud. Estadísticas de la prevalencia de diabetes a nivel mundial. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/index.html. Access date October, 2011.
3. Secretaria de Salud. Numeralia 2008: Diabetes mellitus. Diabetes Hoy 2009;10:2166-2178.
4. Organización Panamericana de la Salud. Adherencia a los tratamientos a largo plazo; pruebas para la acción. Ginebra: OMS; 2004; pp. 1-39, 75-90.
5. Watari K, Letamendi A, Elderkin-Thompson V, Harron E et al. Cognitive function in adults with type 2 diabetes and major depression. Arch Clin Neuropsychol 2006;21:787-796.
6. Munshi M, Grande L, Hayes M, Ayres D et al. Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care 2006;29:1794-1799.
7. Ishizawa L, Kumano H, Sato H, Iwamoto Y. Decreased response inhibition in middle-aged male patients with type 2 diabetes. Biopsychoso Med 2010;4:1-10.
8. Shimada H, Miki T, Tamura A, Ataka S et al. Neuropsychological status of elderly patients with diabetes mellitus. Diabetes Res Clin Pract 2010;87:224-227.
9. Grober E, Hall Ch, Hahn S, Lipton R. Memory impairment and executive dysfunction are associated with inadequately controlled diabetes in older adults. J Prim Care Community Health 2011;2:229-233.
10. Roberts R, Geda Y, Knopman D, Christianson T et al. Duration and severity of diabetes are associated with mild cognitive impairment. Arch Neurol 2008;65:1066-1073.
11. Iype T, Shaji S, Balakrishnan A, Charles D et al. Cognition in type 2 diabetes: association with vascular risk factors, complications of diabetes and depression. Ann Indian Acad Neurol 2009;12:25-27.
12. Hewer W, Mussell M, Rist F, Kulzer B et al. Short-term effects of improved glycemic control on cognitive function in patients with type 2 diabetes. Gerontology 2003;49:86-92.
13. Rosen M, Beauvais J, Rigsby M, Salahi J et al. Neuropsychological correlates of suboptimal adherence to metformin. J Behav Med 2003;4:349-360.
14. Shorr R, de Rekeneire N, Resnick H, Yaffe K et al. Glycemia and cognitive function in older adults using glucose-lowering drugs. J Nutr Health Aging 2006;10:297-301.
15. Ryan Ch, Freed M, Rood J, Cobitz A et al. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care 2006;29:345-351.
16. Den Heijer T, Vermeer S, Van Dijk E, Prins N et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 2003;46:1604-1610.
17. Manshot S, Brands A, van der Grond J, Kessels R et al. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 2006;55:1106-1113.
18. Brands A, Biessels G, Kappelle L, De Haan E et al. Cognitive functioning and brain MRI in patients with type 1 and 2 diabetes mellitus: a comparative study. Dement Geriatr Cogn Dis 2007;23:343-350.
19. Hayashi K, Kurioka S, Yamaguchi T, Morita M et al. Association of cognitive dysfunction with hippocampal atrophy in elderly japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2011;94:180-185.
20. Zhao W, Alkon D. Role of insulin and insulin receptor in learning and memory. Mol Cell Endocrinol 2011;177:125-134.
21. Manschot S, Biessels G, de Valk H, Algra A et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia 2007;50:2388-2397.
22. Cukierman T, Gerstein H, Williamson J. Cognitive decline and dementia in diabetes a systematic overview of prospective observational studies. Diabetologia 2005;42:2460-2469.
23. Rajeev K, Jeffrey C, Looi L. Type 2 diabetes mellitus, cognition and brain in aging: A brief review. Indian J Psychiatry 2009;51:35-38.
24. Luchsinger J, Reitz C, Patel B, Tang M et al. Relation of diabetes to mild cognitive impairment. Arch Neurol 2007:64:570-575.
25. Mejía-Arango S, Miguel-Jaimes A, Villa A, Ruiz-Arregui L et al. Deterioro cognoscitivo y factores asociados en adultos mayores en México. Salud Pública Mex 2007;49:475-480.

26. Yaffe K, Kanaya A, Lindquist K, Simonsick E et al. The metabolic síndrome, inflammation, and risk of cognitive decline. J Am Med Assoc 2004;292:2237-2242.
27. Cervantes A, Rodríguez M, Calleja J, Ramírez J. Función cognitiva en pacientes con diabetes mellitus tipo 2: correlación metabólica y por imagen de resonancia magnética. Med Int Mex 2011;27:217-223.
28. Mejía-Arango S, Zúñiga-Gil C. Diabetes mellitus como factor de riesgo de demencia en la población adulta mayor mexicana. Rev Neurol 2001;53:397-405.
29. Xu W, Qiu Ch, Winblad B, Fratiglioni L. The effect of borderline diabetes on the risk of dementia and Alzheimer disease. Diabetes 2007;56:211-215.
30. Díaz de León E, Barrágan A, Gutiérrez H, Cobos H. Desempeño cognoscitivo y mortalidad en personas mayores de 50 años en México. Rev Panam Salud Pública 2010;27:368-375.
31. Arvanitakis Z, Wilson R, Li Y, Thanik N et al. Diabetes and function in different cognitive systems in older individuals without dementia. Diabetes Care 2006;29:560-565.
32. Zihl J, Schaaf L, Zillmer E. The relationship between adult neuropsychological profiles and diabetic patient´s glycemic control. Appl Neuropsychol 2010;17:44-51.
33. Aberle I, Kliegel M, Zimprich D. Cognitive development in Young-old type 2 diabetes patients: a longitudinal analysis from the "Interdisciplinary longitudinal study of aging". Curr Psychol 2008;27:6-15.
34. Yeung S, Fischer A, Dixon R. Exploring effects of type 2 diabetes on cognitive functioning in older adults. Neuropsychol 2009;23:1-9.
35. Ryan C, Geckle M. Circumscribed cognitive dysfunction in middle-aged adults with type 2 diabetes. Diabetes Care 2000;23:1486-1493.
36. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes and cognitive function. J Clin Exp Neuropsychol 2004;26:1044-1080.
37. McAulay V, Deary I, Ferguson S, Frier B. Acute hypoglycemia in humans causes attentional dysfunction while nonverbal intelligence is preserved. Diabetes Care 2001;24:1745-1750.
38. Galanina N, Surampudi V, Ciltea D, Singh S et al. Blood glucose levels before and after cognitive testing in diabetes mellitus. Exp Aging Res 2008;34:152-161.
39. Décary A, Vendette M, Massicotte J, Mathieu A. A preliminary study of the impact of age-related pathologies on cognitive functioning and waking EEG. N Am J Psychol 2005;7:469-480.
40. Bruce D, Davis W, Casey G, Starstein S et al. Predictors of cognitive decline in older individuals with diabetes. Diabetes Care 2008;31:2103-2107.
41. Hassing L, Hofer S, Nilsson S, Berg S et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. Age Ageing 2004;33:355-361.
42. Ryan C. Diabetes and brain damage: more (or less) than meets the eye? Diabetologia 2006;49:2229-2233.
43. Suzuki M, Umegaki H, Uno T, Oyun O et al. Association between insulin resistance and cognitive function in elderly diabetic patients. Geriatr Gerontol Int 2006;6:254-259.
44. Greenwood C, Kaplan R, Hebblethwaite S. Carbohydrate-induced memory impairment in adults with type 2 diabetes. Diabetes Care 2003;26:1961-1966.
45. Papanikolaou Y, Palmer H, Binns M, Jenkins D et al. Better cognitive performance following a low-glycaemic-index compared with a high-glycaemic-index carbohydrate meal in adults with type 2 diabetes. Diabetologia 2006;49:855-862.
46. Devore E, Stampfer M, Breteler M, Rosner B. Dietary fat intake and cognitive decline in women type 2 diabetes. Diabetes Care 2009;32:635-640.
47. Llewellyn D, Lang I, Langa K, Muniz G et al. Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med 2010;170:1135-1140.
48. NO Brito G. Exercise and cognitive function: a hypothesis for the association of type II diabetes mellitus and Alzheimer´s disease from an evolutionary perspective. Diabetol Metab Syndr 2009;1:1-7.
49. Colberg S, Somma T, Sechrist S. Physical activity participation may offset some of the negative impact of diabetes on cognitive function. J Am Med Dir Assoc 2008;9:434-438.
50. Indelicato J. Association between executive function, physical activity, and physical fitness in people with type 2 diabetes. USA: Northeastern University; 2009.

Declaration of conflict interest: None

Translation of the original version published in spanish in: Salud Mental 2013, Vol. 36 Issue No. 2