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P200 parameters in patients with diabetes mellitus type 2 (DM2)

Oscar H. Hernández[1,2], Luisa Aguirre-Manzo[1], Freddy Ye-Ehuan[1], Rolando García-Martínez[2] and Guadalupe Maldonado-Velázquez[3]*

[1]Hospital General de Especialidades Dr. Javier Buenfil Osorio, Secretaría de Salud; [2]Biomedical Research Center, Universidad Autónoma de Campeche; [3]Faculty of Chemical-Biological Sciences, Universidad Autónoma de Campeche. Campeche, Camp., Mexico

Abstract

Introduction: *A complication underserved in diabetic patients is the cognitive deficits that can reach dementia. Studying the association between electrophysiological, neuropsychological, and biochemical measures could provide a breakthrough in the understanding of this phenomenon.* **Objectives:** *To compare P200 parameters between subjects with and without diabetes mellitus type 2 and to determine their relationship with biochemical and neuropsychological indicators.* **Methods:** *This is an observational, prospective, transversal and analytical study. Seventy-four participants were divided into two groups: 37 with diabetes mellitus type 2, and 37 subjects as controls. P200 latency, amplitude, and rate of rise to somatosensory stimuli were measured and related to the Mini Mental State Examination (MMSE) test and blood glucose and glycosylated hemoglobin.* **Results:** *Diabetics showed longer latency ($p < 0.042$, 1-tail) and lower MMSE score ($p < 0.0001$) than controls. Negative associations of amplitude and rising rate with glycosylated hemoglobin were observed in patients ($p < 0.025$); also, between amplitude and blood glucose ($p < 0.038$, 1-tail) and between MMSE score and time with diabetes mellitus type 2 ($p < 0.007$).* **Conclusions:** *The P200 parameters of the somatosensory system are sensitive to metabolic deterioration of diabetic patients, so its use in monitoring the cognitive state of patients is recommended.* (Gac Med Mex. 2016;152:281-8)

Corresponding author: *Oscar H. Hernández, ohhernan@yahoo.com.mx, ohhernan@uacam.mx*

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Introduction

Currently, there are 347 million people with diabetes estimated in the world, and the number continues to increase, with common complications in different organs[1,2]. Although the effects of diabetes on the peripheral nervous system are well established, the effects of this disease at the central level and on complex neuronal functions are less clear[3-5]. There are numerous evidences associating type 2 diabetes mellitus (DM2) with the appearance of cognitive deterioration (CD) and Alzheimer's disease[6-9] and, therefore, adding CD to the list of DM2 complications has been proposed, together with neuropathy, nephropathy, retinopathy and cardiovascular disease[7]. Even modest effects of diabetes on the cognitive function have significant implications on public health, since the onset of CD can make the patient unable to handle his/her disease, turning into a burden for him/herself, for the family and

Correspondence:
*Oscar H. Hernández
Jefatura de Investigación
Hospital General de Especialidades Dr. Javier Buenfil Osorio
Secretaría de Salud
Av. Lázaro Cárdenas, 208
Campeche, Camp., México
E-mail: ohhernan@yahoo.com.mx
ohhernan@uacam.mx

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society[6]. However, when small cognitive disorders are timely detected, it is possible to implement preventive and therapeutic measures in order to keep the patient from reaching dementia. Unfortunately, cognitive functions are not routinely assessed at primary care centers.

Currently, it is not clear how the disease undermines the intellectual capacity of the diabetic patient[10]. Through epidemiological[11], pathological[12], imaging[13] or clinical studies[14], it has been postulated that cognitive dysfunction can occur by cerebrovascular and/or neurodegenerative mechanisms[10], but the existence of a causality relationship between diabetes and these disorders has not been definitively established[10]; therefore, it is important to advance in the knowledge of the mechanisms of CD development and progression in patients with DM2[9].

The cognitive sphere comprises different domains such as attention, perception, habituation, memory, learning, mental chronometry, intelligence, processing velocity, psychomotor efficiency and other executive functions of the frontal lobe[15], but there is no consensus on which of these domains are most affected by DM2. In this sense, electrophysiological studies have contributed to elucidate the effects of this disease on central neurons through the measurement of long latency evoked potentials or cognitive potentials such as the P300 wave, which is related to attention and short-term memory processes[16,17]. However, few studies have been conducted in diabetic patients and the results are inconsistent, since, in some studies, latency increases in the waves of patients vs. controls are observed[16,18-22], but others fail to find significant differences between groups[23]. Similarly, some report that electrophysiological waves' parameters are correlated with biochemical disturbances of the patients[21], although others have not observed this[18,20]. The vast majority of works with evoked and cognitive potentials have been carried out applying auditory and visual stimuli, but information on somatosensory stimuli is much scarcer. Most reports on somatosensory evoked potentials in diabetic patients have measured short latency components (< 50 ms), since they have focused on the study of peripheral neuropathy[24-28]. However, in addition to clear peripheral anomalies, neuronal damage at the level of the somatosensory cortex has also been found[29,30]

There are no reports on the effects of DM2 on the P200 wave, which is considered to be an endogenous component generated at the frontal associative cortex[31,32]. Recently, P200 has been shown to allow the study of cognitive processes such as habituation, which is dependent on the sensory modality and the measured parameter[33,34]. Hence, somatosensory stimuli produce more habituation in the waves' amplitude and rate of rise than auditory and visual stimuli[33]. P200 rate of rise has also been reported to be more sensitive than latency and amplitude to habituation and to the effect of neuroactive substances such as alcohol[34]. Although the effects of DM2 on the latency and amplitude of some cerebral waves have been studied[21], there are no reports on the effects of this condition on P200 rate of rise.

On the other hand, the presence of CD in diabetic patients has been clearly demonstrated using the Mini-mental State Examination (MMSE), developed by Folstein et al. in 1975[35-38]. The MMSE does not require specialized equipment for its application, it is little time-consuming and it is portable and inexpensive and, therefore, it is considered to be the neuropsychological screening test most widely used in the world for the detection of cognitive dysfunction[39].

Thus, the purpose of this study was to compare cognitive electrophysiological parameters between diabetic patients and controls without DM2 and to determine possible associations with biochemical and neuropsychological indicators. In particular, the way the condition affects P200 wave latency, amplitude and rate of rise in response to somatosensory stimuli was explored, as well as how these parameters relate to the MMSE, glucose (Glu) and glycosylated hemoglobin (HbA1c) values. This information represents an important advance in the knowledge of somatosensory system-associated central neuronal effects of DM2 and opens the possibility to find new indicators to understand the CD appearance and development mechanisms. These indicators will contribute to better monitoring of the condition to eventually act on it and this way prevent, or at least delay, the appearance of dementia.

Materials and methods

Participants

A prospective, cross-sectional, analytical observational study, carried out over the year of 2014 at the Hospital General de Especialidades Dr. Javier Buenfil Osorio (HGEJBO) is presented. Total sample was comprised by 74 male and female participants, divided into 2 groups: 37 adult patients with DM2 and 37 subjects without DM2, who acted as controls. The patients were known at the internal medicine department. The controls

were selected among relatives or patient companions on their visits to the outpatient clinic and showed fasting Glu levels lower than 100 mg/dl. The subjects selected from both groups that agreed to participate on the study stated it by signing an informed consent letter, after having received a thorough explanation on the protocol, which was previously reviewed and approved by the Committee of Ethics in Research of the HGEJBO. Both groups were comparable in socioeconomic characteristics and had no other chronic or degenerative systemic disease. Those with addiction to drugs, as well as pregnant or postmenopausal women on hormone replacement therapy, or those with electrophysiological testing contraindications for any cause were excluded. Subjects with diastolic valued higher than 90 mmHg during the preceding week and/or on the day of assessment were regarded as having uncontrolled hypertension and were also excluded from the study. Patients were included if they had been diagnosed at least one year prior.

Assessments and instruments

Biochemical assessment

Fasting patients were drawn a blood sample from the brachial vein using a conventional technique with Vacutainer®, for the Glu and HbA1c determination (the latter only in patients). The analyses were carried out at the Faculty of Chemical-Biological Sciences of the Universidad Autónoma de Campeche.

Electrophysiological assessment

- Stimulation: The VikingQuestSystem® equipment was used to obtain the P200 wave by applying somatosensory stimuli. Three 64-stimuli series were applied (5-ms duration each) at a frequency of 1/second, which were administered using 2 disc electrodes placed onto the anterior surface of the left wrist with the proximal cathode. In each subject, the sensorial threshold was determined by gradually increasing the intensity, which was established at 1.2-fold said threshold. Intensity was always maintained below the level of pain.
- Record: Each stimuli block produced clear voltage changes that were picked up by the VikingQuest system and analyzed off-line. Electroencephalographic (EEG) records were obtained by means of disc electrodes (Grass F-E5H) fixed onto the scalp. The active electrode was placed at the center of the head (Cz), the reference electrode at the left earlobe and the ground at both ears (10-20 international system). The level of impedance was maintained always below 5kΩ. Three averaged potentials were obtained by applying at least 192 stimuli on each participant. The records with movement artifacts were automatically disregarded and substituted by the system (< 2%). Three parameters were measured for each P200 wave: peak latency in milliseconds (ms), peak-to-peak amplitude in microvolts (μV) and rate of rise in μV/ms. Latency is the time the wave takes to peak, within the interval of 150-250 ms, since the application of the stimulus. Amplitude is the size of the wave measured from N1 to P200. The rate of rise, reported for the first time in diabetic patients, also showed NO between-group differences (DM2: 0.093 ± 0.033 μV/ms; controls: 0.098 ± 0.030 μV/ms; $p > 0.05$).

Neuropsychological assessment

The MMSE test was applied both to patients and control subjects. The MMSE uses a structured scale comprising a maximum of 30 points grouped into 5 categories: orientation (spatial and temporal), immediate repetition, attention/calculation, memory and language. Since the MMSE score is influenced by age and level of education, the correction according to Crum et al.[40] was applied, by adopting the scale suggested by Folstein et al.[41]: normal (≥ 27 points), mild CD (21-26 points), moderate CD (11-20 points) and severe CD (≤ 10 points).

Procedure

The selected patients were instructed to attend the HGEJBO in fasting conditions at 08:00 h. At their arrival, they were briefly reminded of the protocol procedures, weight, height and vital signs were recorded and the blood sample was taken. The patients were provided an energy drink (Glucerna®). Then, they were brought to the electrophysiology area for evoked potentials testing. Subsequently, they were referred to the general waiting area or to the exit.

Data analysis

The data were analyzed using the SPSS v.15 software. A statistical descriptive univariate analysis was carried out with mean values (M) and standard deviation (SD).

Table 1. Mean blood pressure (mBP), heart rate (HR), height, weight , body mass index (BMI) and age mean values (M) and standard deviation (SD) in the control and diabetic (DM2) subjects groups

Variable	Control M (SD)	DM2 M (SD)	p	d
mBP (mmHg)	95.5 (16.4)	95.2 (8.6)	0.92	0.02
HR (beats/min)	73.7 (9.1)	72.3 (8.5)	0.73	0.16
Height (m)	1.58 (0.09)	1.59 (0.09)	0.77	0.11
Weight (kg)	73.5 (13.2)	77.6 (15.9)	0.24	0.28
BMI (kg/m^2)	28.8 (4.6)	30.4 (5.2)	0.16	0.33
Age (years)	47.9 (8.8)	49.6 (7.0)	0.35	0.21

p: between-group alpha level; d: Cohen's d.

Distribution normality was assessed with the Kolmogorov-Smirnov and variance homogeneity with Levene's test. Between-group differences were determined using the Mann-Whitney U-test or Student's t-test for independent samples. Cohen's d was used to calculate the effect size. To assess for possible associations between variables, Pearson's bivariate correlations were used. Statistical significance was established at p-values lower than 0.05. A one-way p-value was sometimes used since it adjusted to the predetermined hypothesis.

Results

Seventy-four subjects were selected, 37 with a diagnosis of DM2 and 37 healthy individuals as controls, all of them recruited at the HGEJBO of the city of San Francisco de Campeche. Out of these, 40 (54.1%) were males and 34 (45.9% were females, with an average age of 48.7 ± 8.0 years. No statistically significant differences (p > 0.05) were observed between groups on age, mean blood pressure (mBP), heart rate (HR), height, weight and body mass index (BMI) (Table 1). Average time with the disease for patients was 10.6 ± 6.2 years, with Glu levels of 176.9 ± 86.2 mg/dl and HbA1c at 8.9 ± 2.3%.

Just as it has been reported for P100 and P300 waves in diabetic patients[20-22, 42-53], P200 also showed a significant delay in peak latency in the group of patients (180.2 ± 32.1 ms) versus controls (166.4 ± 35.5 ms; Fig. 1), but without showing amplitude differences (DM2: 3.53 ± 1.85 µV; controls: 3.64 ± 1.32 µV; p > 0.05). The rate of rise, reported for the first time in diabetic patients, also showed between-group differences (DM2: 0.093 ± 0.033 µV/ms; controls: 0.098 ± 0.030 µV/ms; p > 0.05).

Significant associations were observed in patients between biochemical patterns and P200 amplitude and rate of rise values. In figure 2, it can be appreciated that higher HbA1c levels produce smaller waves (A) and with lower rate of rise (B). A similar pattern was observed in patients, though no in controls, when Glu blood levels were related to P200 amplitude (Fig. 3). The relationship between blood glucose and rate of rise was also negative, although in this case no statistical significance was reached (r = -0.263; p = 0.132). No relationship at all was found between the time with the disease and electrophysiological parameters (ps > 0.173). Relationships between the participant's age and potentials latency or amplitude (p > 0.087) were neither observed, but a positive relationship was obtained

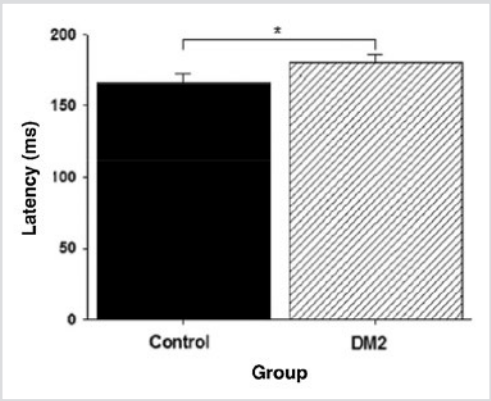

Figure 1. *P200 wave peak latency in diabetic patients (DM2) and controls. A slight but significant increase is observed in the group of patients. Vertical bars are the standard error of the mean. *1-tailed p-value < 0.042. N = 74.*

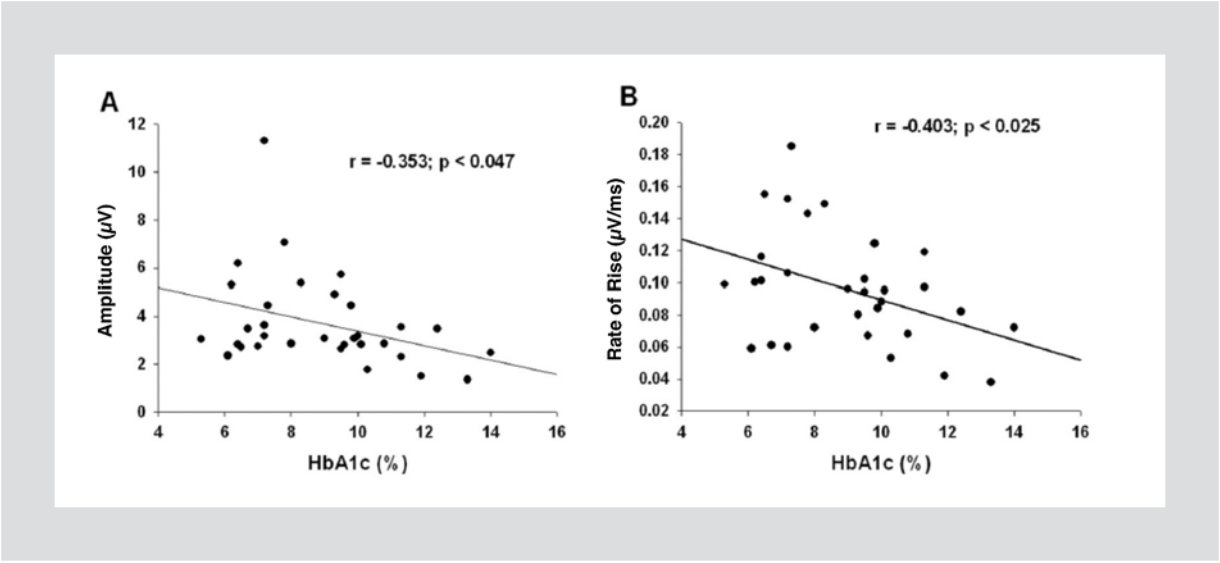

Figure 2. *Negative correlations between the P200 wave amplitude* **(A)** *and rate of rise* **(B)** *and glycosylated hemoglobin (HbA1c) values in diabetic patients. Descending solid lines indicate the least-squares regression adjustment.*

between age and rate of rise (r = 0.340; p < 0.042), but only in the DM2 group.

The MMSE values were adjusted for level of education according to Crum et al.[40]. Figure 4 shows that these were significantly lower (p < 0.0001) in the diabetic patients (26.9 ± 2.1) with regard to subjects in the control group (28.6 ± 1.4), which corresponds to mild CD.

A negative correlation was obtained between the years with diabetes and the MMSE values, in such a way that the longer the time with the disease, the greater the CD (Fig. 5). It is important mentioning that even by suppressing the highest value of 35 years, the tendency was the same, although significance is weakened (r = -0.325; 1-tailed p < 0.027). No significant differences were observed in the MMSE values between male and female subjects in both groups. Neither was a significant association found between the MMSE values and the remaining clinical, biochemical or electrophysiological variables of patients and controls (ps > 0.05).

Discussion

In the present study, electrophysiological, neuropsychological and biochemical tests were applied in adult

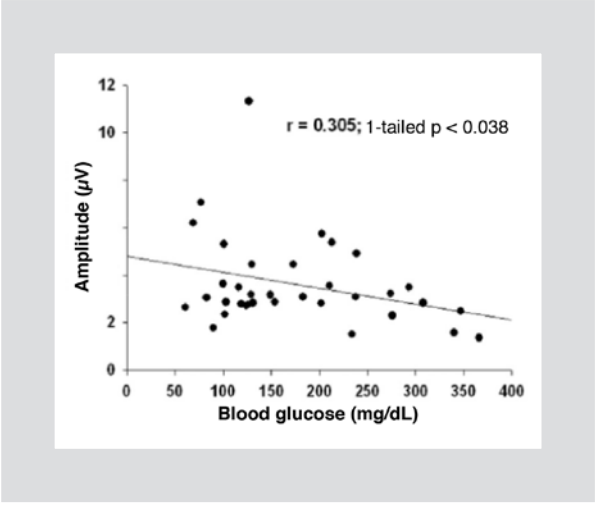

Figure 3. *Negative correlation between P200 wave amplitude and blood glucose values in diabetic patients. Descending solid lines indicate the least-squares regression adjustment.*

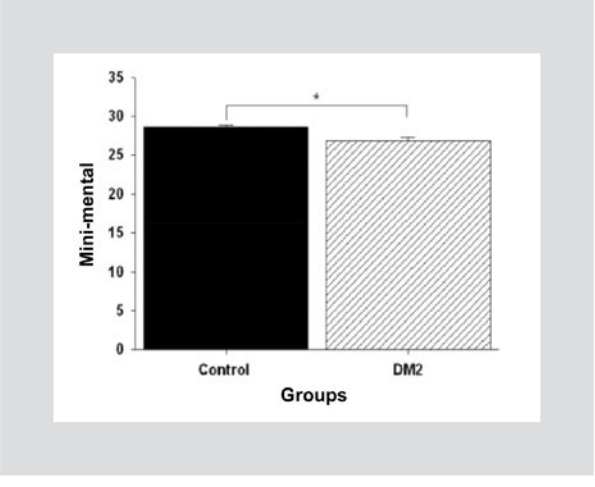

Figure 4. *MMSE test values, both for the control and the diabetic patients (DM2) groups. A significant decrease is observed in the patients' score. Vertical bars are the standard error of the mean. *p < 0.0001. N = 74.*

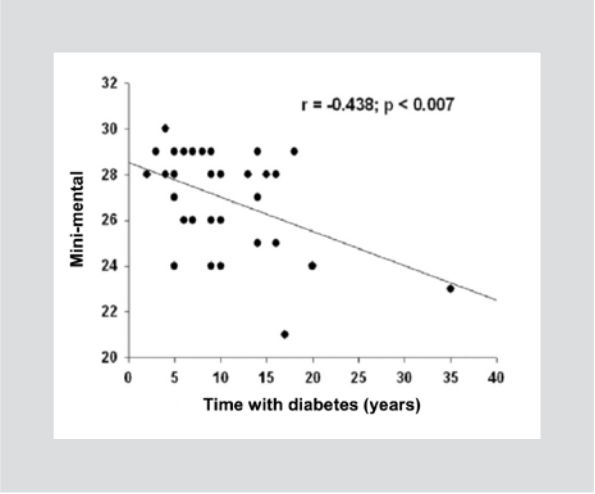

Figure 5. *Relationship between the score obtained on the MMSE and years with the DM2 diagnosis. The negative slope can be clearly observed. The descendent solid line indicates the least-squares regression adjustment.*

subjects with and without DM2 in order to find indicators suggestive of CD. P200 wave parameters are compared for the first time by applying somatosensory stimuli between diabetic and control subjects. P200 is a cognitive wave originating in the frontal associative cortex[31,32], the functional significance of which is not clearly understood but it is associated with the classification of stimuli and with attention-modulated processes (e.g., habituation) that are necessary for sensorial tasks discrimination[34,54]. P200 peak latency showed a significant delay in the group of patients, which reflects a dysfunction in neural processing velocity. Previous studies of sensory or cognitive evoked potentials have also shown a delay in the wave peaks in diabetic patients[20-22,42-53], although other reports indicate similar latencies[23]. However, these works are not entirely comparable with the present study, since they measure short latency sensory waves (N19, P40, P100) or waves with even longer latency (P300). Occasionally, evoked potentials latency increase has been reported in diabetic patients (P100) due to acute hypoglycemia episodes[55]; however, none of the patients in this study showed signs or symptoms of low Glu blood levels during the electrophysiological recordings, which was corroborated by laboratory analyses carried out at the same time. The latency of averaged cerebral waves depends on the conduction distance, diameter of the fibers, presence of myelin and the number of synapses involved in the pathway. This way, latency prolongation can imply alterations at any of these sites. In other chronic diseases such as multiple sclerosis, it is well documented that there is more latency due to alterations at the myelin level. However, in diabetes this issue is less clear, since cerebral macro- and microvascular involvement (with amyloid angiopathy) can cause damage not only on the myelin but on other places of the neural pathways, driving the patient not only to CD but also to Alzheimer[7,11].

In this study, no differences were observed between groups in the waves' amplitude, which is consistent with observations from other reports on P300[16,23], although some of them report less amplitude in diabetic patients[21,46]. Group differences were also no found with regard to the rate of rise.

Although the amplitude and rate of rise were not different in diabetics with regard to control subjects, there was a remarkable inverse correlation shown by the patients' biochemical status, as measured by the levels of HbA1c and blood glucose. Clearly, in the presence of higher metabolic unbalance, P200 is reduced in size and develops more slowly. It is important pointing out that, for the first time, the P200 rate of rise is reported in diabetic patients, which turned out to be more sensitive to blood Glu chronic low levels than amplitude (Fig. 2).

Since amplitude reflects the number of synchronized active fibers and the rate of rise measures recruitment velocity, the decrease of these parameters in uncontrolled diabetics might be due to the toxic effects of chronic hyperglycemia on neurons. At this situation, increased enzyme activity, oxidative stress, presence of free radicals and inflammatory cytokines are known to occur, driving to neural ischemia[18,56-58]. It is also possible for this to be due to extracellular glutamate accumulation, as happens in the retina[59]. This is important, since the somatosensory cortex has been implied in memory functions through glutamatergic thalamocortical inputs and it is also a critical region for the development of Alzheimer[60,61]; therefore, further studies will have to be conducted to corroborate the role of glutamate in the somatosensory cortex of diabetic patients. If the referred metabolic changes affect P200 latency and rate of rise, the structure and function of its neural generators would be sustaining alterations, which imply a certain degree of CD. It is of particular interest for us to find out in diabetic subjects the degree of involvement of some cognitive functions such as habituation, which has been measured with the P200 parameters in healthy subjects[33,34].

Electrophysiological changes in the group of diabetic patients are consistent with the presence of mild CD obtained by the MMSE. Although numerous studies

have demonstrated that diabetes produces cognitive deficit[36-38] that can reach dementia[62], there are also others where no differences have been found between patients and controls[19]. To date, it is not clear if this dysfunction is caused by cerebrovascular or neurodegenerative mechanisms, or a combination of both[9,10], but elucidating this controversy is beyond the scope of the present investigation. Although the score obtained on the MMSE did not turn out to be related to biochemical variables, it did relate to the years of being diabetic, in such a way that the more the time with the disease, the higher the degree of deterioration. It should be emphasized that no correlation at all was observed between the MMSE score and chronologic age, both in patients and controls, which supports the idea that cognitive dysfunction mechanisms present in diabetes are not necessarily equal to those occurring during normal aging.

The alteration of P200 parameters evoked by somatosensory stimuli in diabetic patients offers new opportunities to understand the central effects of the disease, different to those revealed by the study of the P300 cognitive wave, which is obtained by means of "target" stimuli during the oddball paradigm, almost always applying auditory stimuli. Conversely, P200 does not require for this paradigm to be applied, since the potentials are directly obtained ("non-target" stimuli) by means of somatosensory stimuli, which can also be visual or auditory[33]. Somatosensory evoked potentials with early latencies such as N19 (median n.) or P40 (tibial n.) have been useful to demonstrate the damage produced by diabetes on peripheral nerves[22,27-30], but unrelated to cognitive functions. Changes on peripheral electrophysiological components have been observed not to correlate with the metabolic status of diabetic patients or with disease duration and are therefore attributed to a state driven by peripheral neuropathy[28,30].

Although the present investigation shows clear alterations of the P200 wave patterns by applying somatosensory stimuli, it would be convenient to extend these studies to a larger sample of participants, applying other sensorial modalities (visual and auditory) and comparing specific age and gender groups, or those with type 1 diabetes. The conduction of new studies with results consistent with those here obtained will reinforce the use and benefit of long latency somatosensory evoked potentials in the assessment of cognitive functions in diabetic patients. Knowledge on the onset of cognitive deficit during the course of the disease, by means of these indicators, can be highly useful to prevent or delay the onset of dementia, which has a huge negative impact on the patients' quality of life, as well as high cost from the working, institutional and governmental points of view.

In conclusion, this work presents evidence of alterations in the P200 wave parameters, evoked by somatosensory stimuli in diabetic patients, with a delay on the waves' peak and mild cognitive deficit. As metabolic lack of control progresses, the waves' amplitude and rate of rise are reduced, which is consistent with the presence of neuronal damage secondary to chronic hyperglycemia, indicating that maintaining blood Glu and HbA1c levels under control is fundamental.

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