

Case Control Study

## Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes

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### Abstract

#### AIM

To assess the relationship of brain-derived neurotrophic factor (BDNF) with cognitive impairment in patients with type 2 diabetes.

#### METHODS

The study included 40 patients with diabetes mellitus type 2 (DM2), 37 patients with chronic kidney disease in hemodialysis hemodialysis therapy (HD) and 40 healthy subjects. BDNF in serum was quantified by ELISA. The Folstein Mini-Mental State Examination was used to evaluate cognitive impairment.

#### RESULTS

The patients with DM2 and the patients in HD were categorized into two groups, with cognitive impairment and without cognitive impairment. The levels of BDNF showed significant differences between patients with DM2 ( $43.78 \pm 9.05$  vs  $31.55 \pm 10.24$ ,  $P = 0.005$ ). There were no differences between patients in HD ( $11.39 \pm 8.87$  vs  $11.11 \pm 10.64$ ,  $P = 0.77$ ); interestingly, ferritin levels were higher in patients with cognitive impairment ( $1564 \pm 1335$  vs  $664 \pm 484$ ,  $P = 0.001$ ). The comparison

of BDNF values, using a Kruskal Wallis test, between patients with DM2, in HD and healthy controls showed statistical differences ( $P < 0.001$ ).

## CONCLUSION

Low levels of BDNF are associated with cognitive impairment in patients with DM2. The decrease of BDNF occurs early and progressively in patients in HD.

**Key words:** Diabetes mellitus type 2; Hemodialysis; Brain-derived neurotrophic factor; Folstein mini-mental; Premature cognitive impairment

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**Core tip:** The objective was to compare serum levels of brain-derived neurotrophic factor (BDNF) between patients with and without cognitive impairment, patients with diabetes mellitus type 2 (DM2) and chronic kidney disease patients on hemodialysis, in order to increase our knowledge on the possible role of BDNF in early cognitive impairment in DM2. We found differences in serum BDNF levels; they were lowest in patients with DM2 with cognitive impairment. In patients on hemodialysis, serum BDNF levels were lower than in patients with DM2 and healthy controls and ferritin levels were higher in patients with cognitive impairment.

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## INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a growth factor that belongs to the neurotrophin family; its mature isoform binds specifically to the tropomyosin receptor kinase B, a tyrosine kinase receptor, whereas the precursor pro-BDNF binds to the pan-neurotrophin receptor p75NTR; each mediate different neurotrophic signals<sup>[1,2]</sup>. BDNF is also important for learning and memory processes, as it induces long-term potentiation in hippocampus and structural changes in synapses.

A positive correlation between brain BDNF concentration and cognitive performance has been described, while decreased BDNF production has been proposed as one possible pathogenetic factor for Alzheimer's disease and major depression<sup>[3,4]</sup>. Interestingly, plasma BDNF levels are decreased in patients with diabetes mellitus type 2 (DM2) and have been inversely correlated with plasma glucose and insulin resistance as assessed by homeostatic model assessment. Moreover, the output of plasma BDNF from the human brain is abrogated by hyperglycemia, but

it is not regulated by hyperinsulinemia<sup>[5]</sup>.

Zhen *et al*<sup>[6]</sup> found both lower serum BDNF levels and impaired cognitive functions in diabetic patients compared to controls; furthermore, a positive relationship between serum BDNF and delayed memory was observed in diabetic patients, suggesting a role for BDNF in cognitive deficit associated with DM2.

A longer duration of DM2 has been associated with a major risk of chronic kidney disease (CKD), and has been considered a possible new determinant of cognitive decline and dementia<sup>[7]</sup>. Most recent prospective studies have found an association between CKD and cognitive decline<sup>[8-11]</sup>. The Health, Aging, and Body Composition Study demonstrated that more advanced stages of CKD are associated with an increased risk for cognitive impairment<sup>[12]</sup>. BDNF plays a critical role in the functioning of the brain<sup>[13-20]</sup>. It has been observed that the concentration of serum BDNF reflects the changes in brain BDNF levels<sup>[21-23]</sup>; therefore, measuring the concentration of serum BDNF can be used to monitor its changes in the brain<sup>[24]</sup>. It was recently demonstrated that BDNF stimulates the production of prostacyclin in cerebral arteries<sup>[25]</sup>; it plays an important role in endothelium-dependent relaxation and has also antiplatelet, vasculoprotective, cardioprotective and anti-atherogenic properties<sup>[26-28]</sup>. Zoladz *et al*<sup>[29]</sup> demonstrated that the decrease in serum BDNF levels after hemodialysis is accompanied by elevated levels of F-isoprostanes and decreased plasma total antioxidant capacity, which might be caused by the increase in oxidative stress induced by hemodialysis.

The aim of the present study was to compare serum levels of BDNF and the results of the mini mental state examination between patients with DM2 and patients with CKD on hemodialysis, in order to obtain more information on the possible role of BDNF in premature cognitive impairment/dementia in type 2 diabetes. We also investigated whether BDNF predicted premature cognitive impairment, and if it was associated with any clinical parameters in a group of patients with chronic kidney disease.

## MATERIALS AND METHODS

A cross-sectional study was carried out in three groups of patients from the Unidad Médica de Alta Especialidad (UMAE) No. 1 Bajío, Instituto Mexicano del Seguro Social (IMSS), León, Guanajuato, México; the patients were matched by age.

### Patients with DM2

We selected 37 diabetic male patients, aged 39-59 year (mean age  $50.57 \pm 5.9$  year) with a history of DM2 with a duration of  $14.3 \pm 6.22$  year.

### Patients with chronic kidney disease on hemodialysis

We investigated 40 men, aged 18-67 year (mean  $\pm$  SD, mean age  $42.30 \pm 12.8$  years), with chronic kidney disease, who had started hemodialysis therapy (HD).

**Table 1** Clinical characteristics of hemodialysis patients

| Baseline characteristics       | HD patients with cognitive impairment ( <i>n</i> = 17) | HD patients without cognitive impairment ( <i>n</i> = 23) | <i>P</i> |
|--------------------------------|--|---|----------|
| Age (yr)                       | 51.88 ± 12.81  | 42.30 ± 12.87   | 0.02     |
| Duration of hemodialysis (mon) | 41.29 ± 42.01  | 32.08 ± 36.76   | 0.13     |
| BDNF (ng/mL)                   | 11.39 ± 8.87   | 11.11 ± 10.64   | 0.77     |
| Creatinine (mg/dL)             | 8.90 ± 1.90  | 9.21 ± 2.61   | 0.68     |
| Urea (mg/dL)                   | 128.68 ± 54.23   | 127.74 ± 51.54  | 0.77     |
| Hemoglobin (g/dL)              | 12.13 ± 1.38   | 11.53 ± 1.92  | 0.51     |
| Ferritin (ng/mL)               | 1564 ± 1335.05   | 664.22 ± 484.99   | 0.001    |
| Mini-mental state examination  | 19.58 ± 3.24   | 26.08 ± 1.50  | 0.0001   |

BDNF: Brain-derived neurotrophic factor; HD: Hemodialysis therapy.

We excluded patients older than 69 years of age and those with acute infectious diseases, psychiatric diseases or severe liver dysfunction. Baseline demographic and clinical data such as age, primary cause of renal disease and current medications were collected from the patients' records.

### Healthy control subjects

The control group was formed by forty healthy male volunteers from the same demographic group as the patients; they were aged 39-60 years (mean age 42 ± 2.2 year) and received annual health examinations.

Fasting blood samples were collected from patients and healthy controls at 8 am. Serum BDNF concentrations were determined by ELISA using the Human BDNF Quantikine Kit. The concentrations of ferritin in serum and other biochemical parameters were measured at the Central Clinical Laboratory. A neurological assessment was performed before each hemodialysis session (Mini Mental).

The study was performed in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the local Bioethics Committee of the UMAE No. 1 Bajío, IMSS, León, Guanajuato, México. All patients signed an informed consent form for this investigation.

### Statistical analysis

The statistical analysis was performed using Microsoft Excel and Statistica software. The statistical significance of the differences observed between patients and controls was assessed using two-tailed *t*-test,  $\chi^2$  and Kruskal-Wallis (*P* < 0.05).

## RESULTS

The patients with DM2 and on hemodialysis were categorized according to the score obtained in the Folstein Mini-Mental State Examination into a group with cognitive impairment and a group without cognitive impairment. The group of patients with type 2 diabetes and cognitive impairment had 19 patients and the group without cognitive impairment had 18 patients. The average age was 50.57 ± 5.9 years with a history of type 2 diabetes mellitus with a duration of 14.3 ± 6.22 years. We were able to analyze the differences between patients with

and without cognitive impairment (Table 1). We observed significant differences in the levels of glycated Hb, which were higher in patients with cognitive impairment (8.36 ± 1.52 vs 7.33 ± 1.42 *P* = 0.02). There were also differences in the duration of diabetes; patients with cognitive impairment had more years of DM2 (14.31 ± 6.22 vs 9.05 ± 4.64, *P* = 0.007). The values of serum BDNF also showed significant differences between patients with and without cognitive impairment (31.55 ± 10.24 vs 43.78 ± 9.05, *P* = 0.005).

The group of patients on HD with cognitive impairment had 17 patients; the group without cognitive impairment had 23 patients. The average age of the patients was 42.30 ± 12.8 years. The most common cause of renal failure was diabetes mellitus (45%), followed by glomerulonephritis (20%), renal hypoplasia (15%), hypertension (10%) and other causes (10%). Sixty-five point seven percent of the patients had been subjected to a vascular access procedure using a catheter, while only 31.2% had an arteriovenous fistula. There were also significant differences in patients with chronic renal disease on replacement therapy with hemodialysis between those with and without cognitive impairment (Table 2). Ferritin levels were higher in patients with cognitive impairment (1564 ± 1335 vs 664 ± 484, *P* = 0.001), in contrast to serum levels of BDNF (11.39 ± 8.87 vs 11.11 ± 10.64, *P* = 0.77); however, both groups of patients on hemodialysis had lower levels than healthy controls.

The serum BDNF levels of healthy control subjects were 39.36 ± 8.9 ng/mL. The comparison of BDNF levels, using a Kruskal Wallis test, between patients with DM2, HD and healthy controls showed statistically significant differences (*P* < 0.001) (Figure 1).

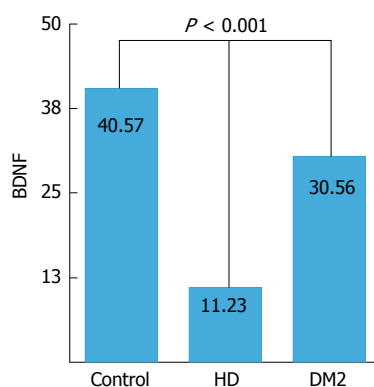
## DISCUSSION

Most recent prospective studies associate chronic kidney disease with cognitive impairment. There has been a significant increase in the prevalence of chronic degenerative diseases worldwide; thus, there is a particular interest in learning how to modify the conditions that cause cognitive decline and dementia. DM2 has been strongly associated with an increased loss of cognitive functions. A recent cohort study showed that high glucose levels may be a risk factor for dementia and

**Table 2 Clinical characteristics of diabetes mellitus type 2 patients**

| Baseline characteristics        | DM2 patients with cognitive impairment ( <i>n</i> = 19) | DM2 patients without cognitive impairment ( <i>n</i> = 18) | <i>P</i> |
|---------------------------------|---|--|----------|
| Age (yr)                        | 50.57 ± 5.90  | 54.05 ± 3.63   | 0.06     |
| Duration of DM2 (yr)            | 14.31 ± 6.22  | 9.05 ± 4.64  | 0.007    |
| BDNF (ng/mL)                    | 31.55 ± 10.24   | 43.78 ± 9.05   | 0.005    |
| Glucose (mg/dL)                 | 177 ± 64.91   | 138 ± 43.90  | 0.07     |
| Glycated hemoglobin (HBA1c) (%) | 8.36 ± 1.52   | 7.33 ± 1.42  | 0.02     |
| Minimetal state examination     | 20.26 ± 2.15  | 25.44 ± 1.50   | 0.0001   |

BDNF: Brain-derived neurotrophic factor; DM2: Diabetes mellitus type 2.



**Figure 1 Difference between serum brain-derived neurotrophic factor levels between control subjects and patients in hemodialysis therapy patients with diabetes mellitus type 2.** BDNF: Brain-derived neurotrophic factor; HD: Hemodialysis therapy; DM2: Diabetes mellitus type 2.

that the combination of DM2 and hypertension greatly increase the risk of cognitive impairment. Beside vascular factors, other risk factors include the formation of advanced glycosylation products, oxidative inflammation and stress, alterations in the hypothalamic-pituitary-adrenal axis and cortisol levels<sup>[30]</sup>, and abnormalities in insulin secretion and signaling that promote cerebral amyloidosis.

The analysis of the relationship between serum ferritin and Mini-Mental scores in HD patients showed a significant difference between serum ferritin levels and the presence of cognitive impairment according to the Folstein test. Therefore, we can say that a higher iron overload corresponds to greater cognitive impairment.

Becerril-Ortega *et al.*<sup>[31]</sup> analyzed the relationship between iron and neurodegenerative diseases (especially Alzheimer's disease) that affect cognitive impairment in a transgenic mouse model; they observed that iron interferes with the processing of the amyloid precursor protein (APP), neuronal signaling and cognitive behavior. The proposed mechanism is that iron overload increases the production of amyloidogenic KPI-APP and amyloid beta; this is mediated by N-methyl-D-aspartate receptors (NMDAR), mainly GluN2B, which is overexpressed. These data suggest that the damage induced by iron overload through APP accelerates cognitive impairment due to excessive extrasynaptic NMDAR activity 30, causing a significant memory and learning deficit, and inhibiting synaptic plasticity, mitochondrial dysfunction and neuronal apoptosis, which can lead to neurodegeneration.

This is also supported by a study that showed evidence of iron overload in brain structures such as the putamen, dentate nucleus, substantia nigra and red nucleus of patients with beta-thalassemia<sup>[32]</sup>. Another group of patients with thalassemia also showed iron overload and increased oxidative damage<sup>[33]</sup>. Blasco *et al.*<sup>[34]</sup> found a significant positive association between obesity, insulin resistance and iron overload in the caudate nucleus, hypothalamus and hippocampus, and poor cognitive performance. Furthermore, it has been shown that iron overload causes oxidative stress *in vitro*<sup>[35]</sup> and can affect the hematopoiesis of bone marrow in mice by increasing oxidative stress<sup>[36]</sup>.

Although there are multiple factors that influence cognitive impairment, several studies have shown an association with circulating levels of BDNF<sup>[37,38]</sup>, and have suggested a synergistic effect between the presence of dementia and BDNF levels in DM2<sup>[39]</sup>. Our study found this association and also that patients on HD had increased oxidative stress, probably induced by iron overload, which was evidenced by elevated levels of ferritin. This was significantly associated with greater cognitive impairment and with serum BDNF levels well below the levels found in patients with type 2 diabetes mellitus and healthy controls.

One of the most common advanced complications of DM2 is CKD. The progressive loss of renal function could make it necessary for the patient to receive renal replacement therapy such as hemodialysis, and the progressive loss of circulating levels of BDNF should be prevented in patients with DM2 to avoid premature cognitive decline. There have been several experimental studies with curcumin<sup>[40]</sup> and resveratrol, both of which increase serum BDNF levels. Curcumin has an antidepressant effect, mediated by its antioxidant activity and up-regulation of phosphor Akt and mTOR levels in the hippocampus and prefrontal cortex<sup>[41]</sup>. Resveratrol has antidepressant-like effects, mediated in part by the normalization of serum corticosterone levels and the up-regulation of Perk, pCREB and BDNF levels in the hippocampus and amygdala<sup>[42]</sup>. This is an alternative that should be investigated further in future randomized clinical trials.

## COMMENTS

### Background

Diabetes mellitus type 2 (DM2) has been strongly associated with an increased



loss of cognitive functions, while decreased brain-derived neurotrophic factor (BDNF) production has been proposed as one possible pathogenetic factor for premature cognitive impairment/dementia. A longer duration of DM2 has been associated with a major risk of chronic kidney disease, and has been considered a possible new determinant of cognitive decline and dementia.

### Research frontiers

The analysis of the relationship between serum ferritin and Mini-Mental scores in hemodialysis therapy (HD) patients showed a significant difference between serum ferritin levels and the presence of cognitive impairment according to the Folstein test. Therefore, the authors can say that a higher iron overload corresponds to greater cognitive impairment, and it is of interest which factors modify the decrement of BDNF production. Measuring the concentration of serum BDNF can be used to monitor its changes in the brain, in order to influence the course of the disease.

### Innovations and breakthroughs

The authors confirm the serum BDNF levels between patients with DM2, HD and healthy controls showed statistically significant differences. Ferritin levels were higher in patients in HD with cognitive impairment, is a breakthrough in the understanding of the factors contributing to the loss of BDNF and cognitive impairment.

### Applications

Monitoring levels of BDNF can prevent cognitive decline implementing new measures such as the use of antioxidants proposed recently and currently under research.

### Peer-review

The study is original and evaluates the cognitive impairment in diabetes mellitus in relationship with the brain-derived neurotrophic factor plasma levels and ferritin. The article has interest and likes suitable for the publication in the Journal.

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