Correlation between vitamin D and serum brain derived neurotropic factor levels in type 2 diabetes mellitus patients

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Abstract. Diabetes Mellitus (DM) currently ranks as the most common endocrine disorder worldwide. Current opinion views DM as a group of heterogeneous metabolic diseases characterized by hyperglycemia triggered by defects in the ability of the body to produce or use insulin in type 1 and 2 DM, respectively. Brain-derived neurotrophic factor (BDNF), one of the neurotrophin family of growth factors, has been linked to the pathogenesis of DM and insulin resistance. Moreover, vitamin D has been associated with insulin resistance and DM. Recently, the interactions between vitamin D and BDNF have been investigated in diabetic rats. However, this correlation has never been investigated in humans. Thus, the aim of the present study was to assess the alterations in serum BDNF and vitamin D levels in T2DM patients in Jordan, prior to and following vitamin D supplementation. A combination of non-experimental case-control and experimental designed studies were utilized to assess the relationship between serum BDNF and vitamin D levels in T2DM patients. The levels of BDNF and vitamin D were measured using commercially available ELISA kits, and fasting blood glucose (FBG) and HbA1c levels were measured in medical labs. The results showed that diabetic patients had lower levels of serum vitamin D and higher levels of BDNF compared with the healthy controls. Moreover, linear regression analysis indicated that BDNF levels were inversely correlated with serum vitamin D levels. Furthermore, vitamin D supplementation significantly increased vitamin D serum levels and decreased BDNF serum levels in diabetic patients. Intriguingly, FBG and HbA1c levels were significantly improved post vitamin D supplementation. These data demonstrate a positive effect of vitamin D supplementation in diabetic patients suggesting the implementation of vitamin D as part of future T2DM treatment plans. However, additional studies are needed to investigate the direct link between vitamin D, BDNF, and T2DM.

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Introduction

Diabetes Mellitus (DM) currently ranks as the most common endocrine disorder. Current opinion views DM as a group of heterogenous metabolic diseases characterized by hyperglycemia, which is triggered by defects in the ability of the body to produce or use insulin in type 1 and type 2 DM, respectively (1,2).

Several predisposing factors have been linked to the pathogenesis of type 2 diabetes mellitus (T2DM), such as obesity, western lifestyles (especially diets), lack of physical activity, genetic predispositions, ethnicity, and inflammation (3). Low-grade inflammation is closely involved in the development of diabetes and its microvascular complications (4). There is a considerable body of evidence supporting the etiological role of inflammatory cytokines in the pathogenesis and prognosis of T2DM (4-7).

Brain-derived neurotrophic factor (BDNF), one of the neurotrophin family of growth factors, is essential for synaptic transmission and plasticity, along with neuronal integrity, survival, growth, and differentiation (8). Shi *et al* (9) reported a rapid increase in the levels of BDNF following exposure of rats to stress. Similarly, Jiang *et al* (10) studied the role of BDNF in rats following an ischemic stroke. Their results showed increases in the levels of BDNF, which subsequently promoted the expression of anti-inflammatory cytokines and inhibited the levels of pro-inflammatory cytokines. These observations reflect the roles of BDNF as a part of a neuronal protective response.

Subsequently, several studies have linked BDNF to systemic inflammatory conditions such as coronary diseases, atherosclerosis, insulin resistance, inflammatory bowel diseases, and the development of diabetes (11-15). *In vivo* studies reported BDNF modulation and changes

in its expression levels as a response to inflammatory conditions (16-18).

Vitamin D, collectively referring to ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), was initially recognized for its role in calcium homeostasis and bone health (19). Subsequently, the extraskeletal roles of vitamin D were studied; studies demonstrated the crucial role of vitamin D in immunoregulation and inflammation. A review by Calton *et al* (20) highlighted the body of evidence on the anti-inflammatory role of vitamin D through its ability to inhibit the proliferation of pro-inflammatory cells and in modulating the production of inflammatory cytokines.

Ojaimi *et al* (21) first reported the role of vitamin D in regulating the levels of pro-inflammatory markers during inflammation in a dose-dependent manner. In their study, supplementation with the optimal dose of vitamin D significantly reduced the levels of inflammatory markers, including that of IL6, TNF, and IFN. Subsequent studies demonstrated similar outcomes in several inflammatory and low-grade inflammation conditions, such as insulin resistance, obesity, and diabetes (20-23).

Recently, Nadimi *et al* (24) investigated the effects of vitamin D supplementation on BDNF levels in diabetic rats. BDNF levels were shown to be positively correlated with vitamin D supplementation in aged rats (25). However, in primary cultures of astrocytes, BDNF levels were not altered by vitamin D supplementation. The interactions between vitamin D and BDNF have never been investigated in humans, to the best of our knowledge. Herein, the alterations in serum BDNF and vitamin D levels in T2DM patients in Jordan were investigated, prior to and following vitamin D supplementation.

Materials and methods

Study design and patient characteristics. The present study was a combination of a non-experimental case-controlled study and an experimentally designed study. The study was approved by the Institutional Review Board of the Jordan University of Science and Technology (approval no. 2019/121/7). The study was conducted at the clinics of King Abdullah University Hospital (KAUH; Irbid, Jordan) between November 2018 and March 2019.

This study included 150 individuals with T2DM and 150 healthy controls. In the T2DM group, 66 of the recruited patients were male with an age range of 39-63 years and a median age of 51 years, and 84 were female, with an age range of 33-69 years and a median age of 53 years. In the control group, 78 of the recruited participants were female with an age range of 39-96 years and a median age of 51, and 72 were male with an age range of 36-64 years and a median age of 50 years. T2DM participants were diagnosed according to the American Diabetes Association guidelines (26) and were recruited during their visit to the Endocrinology and Diabetic clinic of KAUH, and the healthy control group were recruited from other clinics at KAUH. The healthy controls had no signs or symptoms associated with T2DM during their recruitment. Subjects in the study were matched by age and body mass index (BMI) and were required to sign a consent form prior to their enrollment.

For further confirmation of the presence or absence of T2DM, repeated fasting blood glucose (FBG) analysis was performed on all subjects. Pre-diabetic individuals with a repeated FBG of 100-125 mg/dl were excluded from this study. Subjects with chronic kidney or liver diseases that may interfere with vitamin D metabolism were excluded from the study. Subjects with Cushing's syndrome, polycystic ovarian syndrome, thyroid dysfunction, or hyperprolactinemia and subjects who indicated receiving any of the vitamin D pharmacological preparations by mouth or topically were also excluded from the study. Height (cm), weight (kg), and waist circumference (WC) were measured for all subjects during their visit to the hospital. The BMI was calculated using the formula: weight/height^2 (kg/m^2).

Collection of blood and serum samples. Following overnight fasting, a blood sample (5 ml) was withdrawn using a sterile plain tube with a clot activator and gel (AFCO) from each participant. Another sample (5 ml) was withdrawn into an EDTA tube (AFCO). Within 60 min of collection, the blood-containing plain tubes were centrifuged at 4,500 x g for 5 min to separate the serum. Serum samples were aliquoted in three Eppendorf tubes (1.5 ml) and stored at -80˚C until required for measuring the BDNF, vitamin D, and fasting glucose levels. Blood-containing EDTA tubes were used for HbA1c measurements.

Therapeutic interventions. A total of 26 subjects (21 males and 5 females) from the 150 T2DM patients aged between 40 and 77 years old, were confirmed as having low serum levels of vitamin D (<30 ng/ml). These subjects were included for the assessment of vitamin D supplementation.

Vitamin D_3 tablets (weekly dose: 50,000 IU; Biodal) were given for 3 consecutive months (from June to September) for each patient. Before and after the intervention period, plain and EDTA tubes were withdrawn in the morning after overnight fasting. EDTA tubes were used for HbA1c analysis. Serum from the plain tube was used for measuring the levels of BDNF, vitamin D, as well as fasting glucose.

All subjects were instructed not to change their lifestyle during this period, including their dietary habits, medications, daily exposure to the sun as well as daily exercise. Weekly sun exposure and exercise hours were recorded during the intervention period.

Biochemical measurements. Collected serum samples were used for BDNF, 25(OH) vitamin D as well as FBG measurements. Whole blood samples collected in EDTA tubes were used for HbA1c measurements. FBG and HbA1c were measured on a Roche automated clinical analyzer system (Roche Diagnostics GmbH).

The concentrations of 25(OH) vitamin D in serum were measured quantitatively using specific ELISA kits purchased from Abcam (cat. no. ab213966) according to the manufacturer's instructions. For accurate measurement, a 1:10 dilution of samples with Dissociation Buffer was used as described in the assay procedure. Serum BDNF concentrations were measured using an ELISA kit purchased from R&D systems (cat. no. DY248) according to the manufacturer's instructions. Optical density was read spectrophotometrically using an 800TM TS Microplate reader (BioTek Instruments, Inc.) at 405 nm for 25(OH) vitamin D and at 450 nm for BDNF.

Table I. Patient characteristics and the biochemical profile.

Variable	Controls, n=150	Type 2 diabetes mellitus, n=150	P-value[b]
Age, years n (%)			1.0000
<40	7 (4.66%)	7 (4.66%)	
40-49	54 (36.00%)	54 (36.00%)	
50-59	73 (48.67%)	73 (48.67%)	
>60	16 (10.67%)	16 (10.67%)	
Body mass index, kg/m^{2}[c]	31.69±6.28	31.42±5.84	0.7008
Waist circumference, cm[c]	109.86±10.03	108.59±12.22	0.3248
Glucose, mg/dl[c]	93.20±10.43	205.20±95.76	<0.0001[a]
HbA1c (%)[c]	5.05±1.28	7.54±1.87	<0.0001[a]

[a]P≤0.0001. [b]Unpaired Student's t-test. [c]Data are presented as the mean ± standard deviation.

Statistical analysis. All statistical analyses were performed using SPSS version 22 (IBM Corp). Figures were generated using GraphPad Prism version 8.0.2 (GraphPad Software, Inc.). Differences in serum 25(OH) vitamin D and BDNF levels between the healthy controls and T2DM cases, in addition to biochemical parameters and indices for the pre- and post-supplementation subjects were evaluated using a paired Student's t-test. P<0.05 was considered to indicate a statistically significant difference. Moreover, linear regression analysis was performed to determine the association between 25(OH) vitamin D levels and BDNF levels.

Results

Subject characteristics and the biochemical profile. The baseline characteristics and biochemical profiles of the study subjects are presented in Table I. Data are presented as the mean ± SD. There were no significant differences observed with regard to age, BMI, and WC between the two groups (P=1.000, 0.7008, and 0.3248, respectively). The T2DM cases had significantly higher levels of FBG (P<0.0001) as well as HbA1c levels (P<0.0001) compared with the healthy controls.

Serum 25(OH) vitamin D and BDNF levels between healthy controls and T2DM cases. T2DM cases had significantly lower levels of serum 25(OH) vitamin D compared with the healthy controls with mean ± SEM values of 9.14±0.69 and 12.17±12.5 ng/ml, respectively (P=0.0349, Fig. 1A). Moreover, a significant difference was observed in the BDNF concentrations between the two groups (P<0.0001, Fig. 1B). Specifically, the T2DM cases had a higher BDNF level (390.8+10.4 pg/ml) compared with the healthy controls (329.7+9.9 pg/ml).

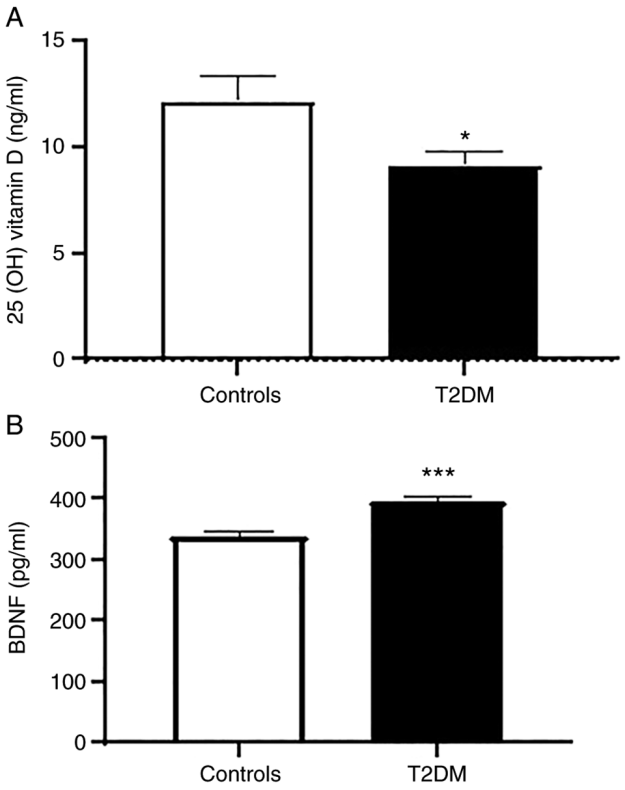

Figure 1. 25(OH) vitamin D and BDNF levels. (A) Serum 25(OH) vitamin D between healthy controls and T2DM patients. The mean ± SEM values of serum 25(OH) vitamin D levels were 12.17±1.25 and 9.14±0.69 ng/ml in the healthy controls and T2DM patients, respectively (P=0.0349). (B) Serum BDNF levels between healthy controls and T2DM. The mean ± SEM values of BDNF levels were 329.7+9.9 and 390.8+10.4 pg/ml in the healthy controls and T2DM patients, respectively (P<0.0001). *P<0.05, ***P<0.001. T2DM, type 2 diabetes mellitus; BDNF, brain-derived neurotrophic factor.

Correlation between BDNF and 25(OH) vitamin D levels in the serum. Fig. 2 shows the significant negative correlation observed between the BDNF levels and 25(OH) vitamin D levels in the serum (P=0.0333, based on linear regression analysis).

Vitamin D intervention. Based on the above results showing significantly lower levels of 25(OH) vitamin D and higher BDNF levels in the serum of T2DM cases, along with the significant negative correlation between BDNF levels and 25(OH) vitamin D levels in the serum, it was hypothesized that vitamin D supplementation may be helpful in improving BDNF levels.

Following the end of the administration period, the levels of 25(OH) vitamin D were significantly increased in the post-supplementation measurements compared with the

Table II. Biochemical parameters before and after vitamin D supplementation.

Variable	Pre-supplementation[d]	Post-supplementation[d]	P-value[c]
25(OH) vitamin D (ng/ml)	1.35±0.82	34.82±16.98	<0.0001[b]
Glucose, mg/dl	214.68±78.00	182.79±65.76	0.0324
HbA1c (%)	8.29±1.90	7.54±1.42	0.0195[a]
Brain derived neurotrophic factor, pg/ml	383.65±91.35	247.22±113.66	<0.0001[b]

[a]P<0.05, [b]P<0.0001. [c]Paired Student's t-test. [d]Data are presented as the mean ± standard deviation.

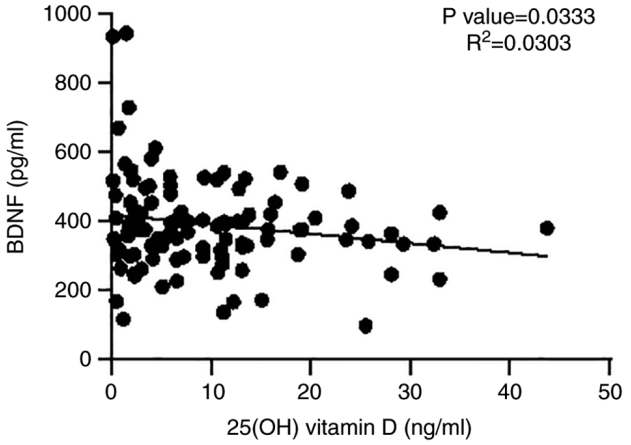

Figure 2. The correlation between serum BDNF levels and 25(OH) vitamin D levels. There was a significant negative correlation between BDNF levels and 25(OH) vitamin D levels in the serum of the type 2 diabetes mellitus patients (P=0.0333). BDNF, brain-derived neurotrophic factor.

pre-supplementation measurements (P<0.0001), highlighting the adequacy of the treatment. Interestingly, supplementation resulted in a significant reduction in the BDNF levels (P<0.0001), FBG levels (P=0.0324), and HbA1c levels (P=0.0195, Table II).

Discussion

In the present study, it was demonstrated that diabetic patients had lower levels of serum 25(OH) vitamin D and higher levels of BDNF compared with the healthy controls. Moreover, linear regression analysis indicated that BDNF levels were inversely correlated with serum 25(OH) vitamin D levels. Furthermore, vitamin D supplementation significantly improved 25(OH) vitamin D serum levels and decreased BDNF serum levels in diabetic patients. Intriguingly, FBG and HbA1c levels were also significantly improved by vitamin D supplementation.

The relationship between diabetes and inflammation is well-established. Inflammatory cytokines such as TNF-α and IL-6, amongst several others, are elevated in T2DM patients (27). Diabetes predisposing factors such as obesity and a sedentary lifestyle result in the continuous presence of a low level of inflammation that affects insulin sensitivity and contributes to the pathogenesis of T2DM (27,28). Vitamin D exerts an essential role in modulating and regulating the immune system and body inflammation. A strong body of evidence indicates that 25(OH) vitamin D exerts regulatory effects on innate and specific immunity (22). Vitamin D is essential for anti-inflammatory responses produced by human immune monocytes (20). Inadequate vitamin D levels are commonly associated with obesity-related continuous diseases that in turn are associated with chronic low-grade inflammation (20,22,23). Here, it was shown that individuals with a confirmed T2DM diagnosis had lower levels of serum 25(OH) vitamin D, and interestingly treating these patients for 3 consecutive months with oral vitamin D supplements improved the blood glucose lab results. These results suggest that monitoring and adjusting vitamin D levels play a crucial role in treating T2DM. Several studies have highlighted the importance of vitamin D in the pathogenesis of T2DM. Vitamin D stimulates insulin release from pancreatic β-cells and low levels of vitamin D as seen in hyperthyroidism have been implicated in the impairment of insulin release from pancreatic cells (23).

Chronic inflammation has been linked to disruption of the neurotrophin family of growth factors, particularly BDNF. In the present study, BDNF levels were higher in T2DM serum samples, suggesting that BDNF is involved in the pathogenesis of T2DM. This contribution may be explained by the chronic inflammation that accompanies T2DM and is considered one of the main pathological factors to T2DM. Alterations in BDNF levels are associated with a myriad of systemic inflammatory conditions such as coronary diseases, atherosclerosis, insulin resistance, inflammatory bowel diseases, airway inflammation, and the development of diabetes (10,29,30). Contrary to the results of the present study, lower serum BDNF levels in T2DM patients have been reported previously (30). There is a large body of evidence that supports the role of BDNF in pathologies that involve inflammation and neuronal impairment such as diabetes (31,32). However, the alterations in BDNF levels and how the body manages the changes in such conditions are not completely understood. For example, BDNF serum levels have been reported to be reduced during neurodegenerative diseases according to several reports (32,33), whilst other reports have reported increases in its levels (31). The increased levels of serum BDNF reported in the present may reflect the differences in the inclusion criteria of diabetic patients and the extent of neuronal involvement. The severity of neuronal impairment accounts for differences in BDNF serum levels (32,34). T2DM is strongly associated with a reduction in cognition (33,35). Cognition impairment in T2DM may occur during the early stages of development and may then be further aggravated with time. Thus, the increased serum BDNF levels could represent

a compensatory mechanism to rescue neuronal damage and to ameliorate cognitive impairment. Further studies should be performed to classify diabetic patients according to the neuronal involvement and to assess the role of BDNF during the different stages of the disease.

Vitamin D supplementation resulted in a significant reduction in BDNF serum levels in the T2DM patients. The available data regarding the effect of vitamin D on BDNF levels are contradictory; some reports indicate a positive effect, others have indicated a negative effect and others yet have reported no effect (24,25,36). In support of the results of the present study, BDNF levels were altered by vitamin D treatment in several reports (35,37,38). Babaei *et al* (35) showed that serum BDNF levels were significantly higher in vitamin D deficient rats and were increased after 25(OH) vitamin D intervention. The results of the present study are in accordance with a report describing a reduction in plasma nerve growth factor and BDNF levels subsequent to vitamin D supplementation in healthy postmenopausal females (39). The increase in serum BDNF levels in vitamin D deficient diabetic patients may reflect a BDNF compensatory mechanism to counteract neuropathies that are associated with the disease; however, additional studies are required to test this theory.

In conclusion, vitamin D insufficiency/deficiency aggravates metabolic syndrome components in diabetic patients and supplementation significantly ameliorates aberrant FBG and HbA1c levels parallel with a reduction in circulating BDNF levels. These data demonstrate a positive effect of vitamin D supplementation in diabetic patients, suggesting the implementation of vitamin D as part of a standard T2DM treatment plan. However, additional studies are required to investigate the direct link between vitamin D, inflammation, BDNF, and T2DM.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author on reasonable request.

Authors' contributions

MAlqudah, MK, MAA and AAD designed the study and analyzed the data. MK and MAA performed the experiments. OAS, DGAU and MK reviewed the analysis and formatted the manuscript. MAlqudah, DGAU, MAllouh and MK wrote the manuscript. MAlqudah performed the statistical analysis. MAlqudah, MAllouh and MAA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethical approval consent to participate

The study was approved by the Institutional Review Board of the Jordan University of Science and Technology (approval no. 2019/121/7) and informed consent was obtained from all participants.

Patient consent for publication

Informed consent was obtained from all participants for publication of their data.

Competing interests

The authors declare that they have no competing interests.

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