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# Attenuated brain derived neurotrophic factor and depression in type 2 diabetes mellitus patients: A case-control study

Rizwana Parveen [a,c], Prem Kapur [b], Sunil Kohli [b], Nidhi Bharal Agarwal [c,*]

[a] Pharmaceutical Medicine, Department of Pharmacology, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, 110062, India
[b] Hamdard Institute of Medical Sciences and Research, HAH Centenary Hospital, Jamia Hamdard, New Delhi, 110062, India
[c] Centre for Translational and Clinical Research, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi, 110062, India

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ABSTRACT

*Problem considered:* Type 2 diabetes mellitus (T2DM) and depression are two of the most prevalent chronic and devastating diseases. Brain derived neurotrophic factor (BDNF) is postulated to modulate the secretion and actions of insulin. Furthermore, a strong association has been demonstrated between BDNF and depression. Although depression is a common neuropsychiatric comorbidity of T2DM, the association of BDNF levels with depression in T2DM remains unclear. Thus, the purpose of the present study was to assess the serum BDNF levels in healthy controls and T2DM patients and explore the association of serum BDNF levels with depression in T2DM patients.

*Methods:* In this study depression was assessed using Patient Health Questionnaire-9 (PHQ-9) and serum BDNF levels were estimated by ELISA technology.

*Results:* and conclusions: A total of 88 subjects were included in the study. The mean PHQ-9 score for T2DM patients (3.91 ± 5.88) was higher than in healthy subjects (1.02 ± 3.02), $p = 0.031$. Subsequently, the prevalence of depression was higher in T2DM patients 16 (36.36%) as compared to healthy subjects 5 (11.36%), $p < 0.001$. The serum level of BDNF was lower in T2DM patients (15.17 ± 2.81 ng/ml) than in healthy subjects (24.65 ± 13.81 ng/ml) than, $p < 0.0001$. Additionally, serum BDNF levels were lower in T2DM patients with depression (13.87 ± 2.62 ng/ml) than in those without depression (15.92 ± 2.77 ng/ml), $p = 0.02$. An inverse association was found between BDNF levels and PHQ-9 scores ($r^2 = 0.2003$, $p = 0.002$). The results suggest that BDNF might influence the presence of depression in T2DM patients. However, further studies are warranted to elucidate the mechanism by which BDNF may influences depression in T2DM patients.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) and depression are two of the most prevalent chronic and devastating diseases.[1] As per International Diabetes Federation, 463 million adults had diabetes in 2019, which is estimated to increase to 700 million by 2045.[2] It has been predicted that by 2030, depression will be the leading disease with 6.3% of the overall disease burden, while, diabetes will be at 10th place with 2.3% of the overall disease burden.[3] As evident by the epidemiological data, approximately 26–30% of diabetics suffer from depression of differential severity.[1] Additionally, clinical study suggest that the presence T2DM doubles the risk of developing depression.[4] Moreover, higher prevalence of depression has been reported in T2DM patients as compared to non-diabetic subjects in several clinical studies.[3,4] This comorbidity is suggested to be a significant barrier in efficient management of T2DM.[4]

Pre-clinical studies have demonstrated that administration of BDNF to diabetic mice is associated with enhancement in glucose[1,5] and lipid metabolism and reduced food consumption.[1] Additionally, expenditure of excess energy was enhanced in db/db mice following BDNF administration.[6] It has been postulated that BDNF influences T2DM pathobiology through modulating the secretion and actions of insulin, ghrelin, neurotransmitters, peptides, leptin, and pro-inflammatory cytokines related to energy homeostasis.[7] Variation in BDNF level has been proposed to affect the prevalence of T2DM.[8] Several case-control studies have demonstrated higher BDNF levels in T2DM patients as compared to healthy controls.[9,10] A cross-sectional study conducted on newly diagnosed T2DM female patients reported increased BDNF levels than female subjects with normal glucose tolerance.[8] Contrary to these reports,

* Corresponding author.
*E-mail address:* nidhi.bharal@gmail.com (N.B. Agarwal).

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several clinical studies have demonstrated lower BDNF levels in T2DM patients as compared to controls.[1,6,11,12] The clinical reports suggest a role of BDNF in T2DM, however, inconsistent findings[13,14] highlight the need for further investigations.

Furthermore, a strong association has been demonstrated between BDNF and depression.[7] Clinical studies have demonstrated significantly lower serum BDNF levels in depressive patients compared with normal controls. A case control study demonstrated lower platelet BDNF levels in patients with major depressive disorder than in healthy subjects.[15] Another case control study showed decreased BDNF mRNA levels in drug-free depressed patients and this deficit was found to be reversed by a 12-week escitalopram treatment.[16] Moreover, use of antidepressants has been shown to up regulate BDNF in the hippocampus of depressive subjects. Additionally, pre-clinical studies have revealed an antidepressant effect of infusion of recombinant BDNF.[1] In spite of the evidence that depression is epidemiologically associated with T2DM, the cause of this correlation is still unclear.[7] Clinical reports have shown that BDNF has a significant role in the pathogenesis of depression and T2DM. Thus, BDNF has been suggested to have an important role linking depression and T2DM.[17,18] However, only few studies have explored the difference in BDNF levels between T2DM patients with and without depression.[7] A case control study revealed no significant difference in serum BDNF levels in T2DM patients with and without depressive symptoms.[7] However, another case control study demonstrated significantly lower BDNF levels in T2DM patients with depression as compared to those without depression.[1] Although depression is a common neuropsychiatric comorbidity of T2DM, the association of BDNF levels with depression in T2DM remains unclear.[1,7]

Thus, additional research is warranted to affirm the association between BDNF and depression in T2DM.[17] Thus, based on the literature, the purpose of the present study was to assess the serum BDNF levels in healthy controls and T2DM patients and explore the association of serum BDNF levels with depression in T2DM patients.

## 2. Material and methods

### 2.1. Subjects

We conducted a case-control study that recruited T2DM patients and healthy controls. Men and women aged ≥18-≤65 years and who agreed to give written informed consent were included. Patients diagnosed with T2DM were included as cases. Healthy subjects were included as controls. We excluded patients with T1DM, a history of severe psychiatric disorders (eg; severe depression, schizophrenia, bipolar disorder), taking any substance of abuse (eg; alcohol, smoking), severe complications of diabetes (i.e., amputation, blindness, renal insufficiency and dialysis), hypertension, liver disease, renal disease, primary hyperparathyroidism, cancer, HIV and obesity, already on any psychotropic drug, women who were pregnant or taking oral contraceptive pills, taking vitamin-D supplement and those who were not willing to give written informed consent. Healthy subjects taking vitamin-D supplement and unwilling to give written informed consent were excluded. One hundred eighty consecutive subjects visiting Diabetic clinic and Medicine OPD were approached for participation. This study was conducted in Hakeem Abdul Hameed Centenary Hospital. The study was approved by the Institutional Review Board. Written informed consent was obtained from the subjects.

### 2.2. Clinical data

A standard format was used for the documentation of demographic factors of the subjects. Body mass index (BMI) was calculated using the measured weight and height for each subject. Detailed medical and family history of the subjects was recorded. The recorded information included diabetes duration, and current treatment for diabetes, family history of diabetes, co-morbid diseases of the patient and their treatment. HbA1c and fasting blood glucose (FPG) were also recorded. Available medical prescriptions and laboratory reports of the healthy subjects obtained through their health checkup were accessed to confirm their eligibility for enrollment.

### 2.3. Assessment of depression

Depression was assessed using Patient Health Questionnaire-9 (PHQ-9). PHQ-9 is easy to use and can be self-administered. It is a brief questionnaire scoring the nine DSM-IV criteria for depression from 0 (not at all) to 3 (nearly every day). PHQ-9 was completed by the subjects after obtaining informed consent at the initial visit. For diagnosing depression, the PHQ-9 was scored as follows: 0–4, no depression; 5–9, mild depression; 10–14, moderate depression; 15–19, moderately severe depression; and 20–27, severe depression.[4]

### 2.4. Serum BDNF analysis

A 5-mL blood was collected in plain vials from each participant. Samples were centrifuged to separate serum at 3000 rpm for 20 min. Serum was stored in aliquots and stored at −80 °C until analysis. BDNF levels were quantified for each serum sample using a highly sensitive ELISA kit (RayBio® ELISA Kits, Norcross, GA), as per the manufacturer instructions.

### 2.5. Statistical analysis

Data contained both continuous and categorical variables. Therefore, quantitative variables are expressed as mean (standard deviation [SD]). Normality of the continuous variables were tested by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Association between two continuous variables were assessed by the Student's 't' test or Mann–Whitney *U* test (for non-normal variables). $\chi 2$ and Fisher exact tests were used to compare differences in the frequencies of categorical variables. For all statistical tests a two-sided p-value $<0.05$ was considered as the level of significance. All statistical analyses were performed using IBM SPSS (version 22.0, IBM Corp., Armonk, NY, USA) software.

### 2.6. Ethics

The study was conducted in agreement with the Declaration of Helsinki and approved by the Institutional Review Board.

## 3. Results and discussion

### 3.1. Baseline characteristics

A total of 88 subjects were enrolled. The study comprised of two groups: cases (patients diagnosed with T2DM) and controls (healthy individuals). Thus, 44 subjects in each group were included. Out of 88 subjects, 42 (47.72%) were females and 46 (52.27%) were males. The mean ± SD age of cases and controls was 45.70 ± 7.53 and 44.91 ± 6.05 years, respectively. Cases had a known T2DM of mean duration 5.42 ± 5.36 years. There was no significant difference in mean age, gender distribution, time spent on exercise or in sun between diabetics and controls. The sociodemographic characteristics of study participants are shown in Table 1.

### 3.2. Assessment of depression

The mean PHQ-9 score for cases (3.91 ± 5.88) was significantly higher than in the controls (1.02 ± 3.02), $U = 715.50$, $p = 0.031$. Additionally, the prevalence of depression was significantly higher in cases 16 (36.36%) as compared to controls 5 (11.36%), (OR: 4.4571, 95%CI: 1.4610–13.5978; p = 0.008). No association was found between depression and age, FPG, HbA1c and duration of disease.

**Table 1**
Subject demographics.

| Characteristic | | Cases (N = 44) | Controls (N = 44) |
|---|---|---|---|
| **Age (years)** | | 46.10 ± 8.64 | 46.01 ± 7.06 |
| **Sex** | Female | 23 (52.27) | 19 (43.18) |
| | Male | 21 (47.73) | 25 (56.82) |
| **BMI (kg/m$^2$)** | | 27.2 ± 3.62 | 26.44 ± 3.80 |
| **FPG (mg/dL)** | | 189.57 ± 95.05 | 86.42 ± 7.43 |
| **Duration of diabetes (years)** | | 6.53 ± 3.47 | – |

n, number; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.
Data is presented as mean ± SD or n (%).

### 3.3. Assessment of serum BDNF levels

The serum level of BDNF was significantly higher in controls (24.65 ± 13.81 ng/ml) than in cases (15.17 ± 2.81 ng/ml), $t = 4.467$, $p < 0.0001$ (Fig. 1). No association was found between BDNF levels, age, gender, FPG and HbA1c.

Association of serum BDNF levels and PHQ-9 scores.

Serum BDNF levels were significantly lower in cases with depression (13.87 ± 2.62 ng/ml) than in cases without depression (15.92 ± 2.77 ng/ml), $t = 2.409$, p = 0.02 (Fig. 2). Moreover, BDNF levels inversely correlated with PHQ-9 scores ($r^2 = 0.2003$, $p = 0.002$) in cases (Fig. 3). No significant correlation was observed in BDNF levels with PHQ-9 scores in controls.

In the present study, the association of BDNF and depression in patients with T2DM was determined. The results of the present study reveal that the prevalence of depression in T2DM patients is higher than in healthy individuals. Moreover, depression was more prevalent in women than in men. Additionally, unemployment was also found to be associated with depression. These findings are supported by clinical studies that have reported similar results. Identical clinical studies have demonstrated a higher prevalence of depression in patients with T2DM.[4,19] A prospective longitudinal study demonstrated higher incidence of depression in patients with diabetes compared to subjects with no diabetes.[20] Further, a recent cross-sectional study demonstrated depressive symptoms to be common in patients with diabetes.[21] Additionally, another cross-sectional study revealed high prevalence of major depressive disorder in patients with T2DM.[22] Similar to our results, a study reported higher prevalence of depression in women than in men. Additionally, no association between depression and duration of diabetes and HbA1c was found.[19] Further, a cross sectional study revealed higher prevalence of depression in females, less educated and unemployed patients.[23]

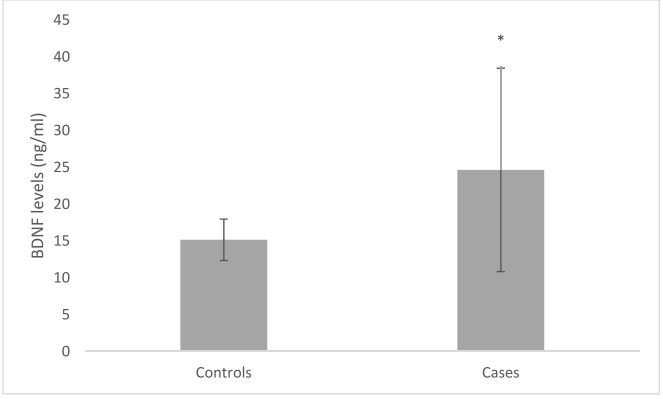


**Fig. 1.** Levels of BDNF in controls and cases
BDNF, brain derived neurotrophic factor. *$p < 0.0001$.

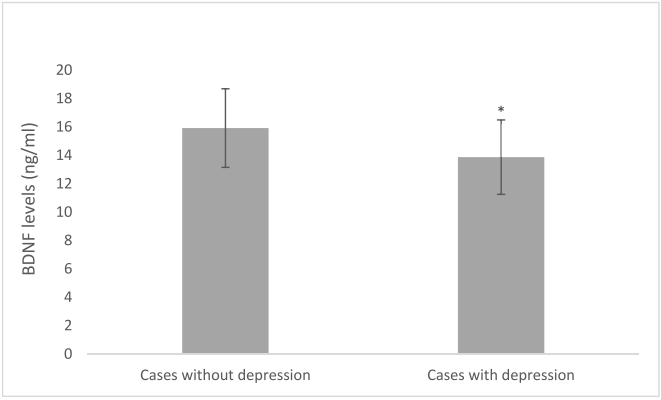


**Fig. 2.** Levels of BDNF in cases with and without depression.
BDNF, brain derived neurotrophic factor. *$p = 0.02$.

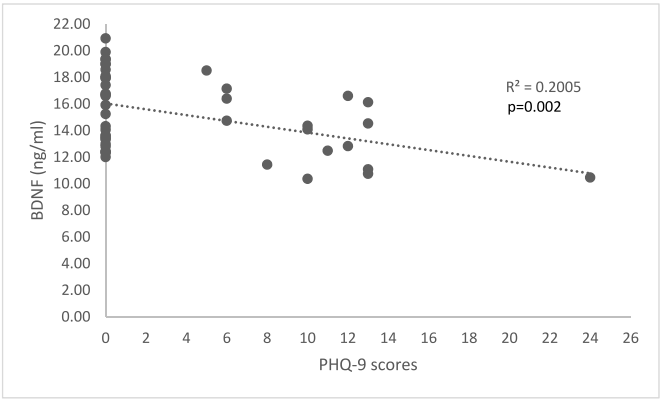


**Fig. 3.** Relationship between brain derived neurotrophic factor and PHQ-9 scores in cases.
BDNF, brain derived neurotrophic factor; PHQ, patient health questionnaire.

The present study found significantly lower serum BDNF levels in patients with T2DM than in healthy controls. BDNF was not associated with HbA1c, FPG or duration of diabetes in the current study. In line with our findings, Fujinami et al. found lower levels of BDNF in diabetics as compared to controls. Additionally, no association was found between duration of diabetes, FPG, HbA1c and BDNF.[6] Several other reports have also demonstrated lower levels of BDNF in T2DM patients as compared to controls.[7,24,25] A recent study revealed decline in serum BDNF levels in diabetics as compared with non-diabetics.[12] Additionally, Krebbe et al. found significantly lower BDNF levels in diabetics and demonstrated reduced output of BDNF from the human brain on elevation of blood glucose levels in healthy individuals.[26] Moreover, an animal study has demonstrated that intermittent administration of BDNF protected the development of T2DM in db/db mice.[27] These findings indicate that T2DM does influence the levels of BDNF. Various mechanisms have been suggested to link BDNF and development of type 2 diabetes. BDNF has been demonstrated to modulate the secretion and actions of insulin, leptin, ghrelin, various neurotransmitters and peptides, and pro-inflammatory cytokines related to energy homeostasis.[19] Further, animal experiments have demonstrated that BDNF might facilitate insulin resistance and dyslipidemia by suppressing PPAR-alpha and fibroblast growth factor 21, resulting in its anti-diabetic effects.[10]

The results of this study showed that the serum BDNF levels in T2DM patients with depressive symptoms were lower than those without depressive symptoms. There were no statistical differences in age, FPG, HbA1c and duration of diabetes between depressed and non-depressed patients. There is scarce and inconsistent evidence regarding the relationship between depression in T2DM and BDNF. Zhou et al. reported a

significantly higher serum BDNF levels in non-depressed T2DM patients as compared to depressed patients, but lower BDNF levels than healthy controls. Additionally, no statistical differences in age and duration of diabetes between depressed and non-depressed patients was found.[1] On the other hand, Wang et al. reported lower BDNF levels in T2DM patients with and without depressive symptoms than in normal controls, however, no significant difference in BDNF levels was observed between T2DM patients with and without depressive symptoms. However, T2DM patients with depressive symptoms had longer duration of diabetes than patients without depressive symptoms.[7] Emerging evidence suggest that T2DM patients with depression have lower serum BDNF levels, suggesting an influence of BDNF on depression in T2DM patients.[28]

In patients with DM and depressive disorders, a wide variety of disturbances may affect the central nervous systems, including the overactivation of the HPA axis, decreased monoamine neurotransmitters, and dysfunctional brain-derived neurotrophic factor.[29] Several mechanisms have been suggested by which BDNF influences depression in T2DM. Since BDNF forms have opposing effects on cell survival, 'yin and yang' model of neurotrophin action has been suggested. Hippocampal p75 neurotrophin receptor ($p75^{NTR}$) activated c-Jun N-terminal kinase (JNK)-Bax signaling leads to neuronal apoptosis, while the tropomyosin receptor kinase B-extracellular-signal-regulated kinase-cAMP response element binding protein (TrkB-ERK-CREB) pathway mediates cell survival and has an important role in antidepressant effects. A study on rats demonstrated that the pro-survival pathway was impaired however, pro-apoptotic pathway remained unchanged.[30] Additionally, TrkB, p-ERK and p-CREB were found to be repressed in the diabetic hippocampus in other animal studies.[31,32] A study in diabetic rats showed higher expression of Bcl2 in diabetic rats treated with Angiotensin-converting enzyme inhibitors (ACEi) or mineralocorticoid receptor (MR) antagonists. These results highlighted that activated BDNF-mediated pro-survival pathway contributes to hippocampal plasticity and thus moderates depressive-like behavior. It is suggested that diabetes-induced neuroinflammation decreases BDNF level, which contributes to neuronal damage and subsequently to the development of depression-like behavior.[30]

### 3.4. Limitations

Our study had several limitations that needs to be mentioned. Some of the data such as duration of T2DM, education status and family history were self-reported or were obtained from subject's medical records. This could have led to recall bias. Next, no causal relationship could be inferred. Additionally, the effect of antidiabetic medication was not assessed. Lastly, the sample size was small which might not represent all T2DM patients.

### 3.5. Future directions

The study demonstrates that BDNF could be a possible serum biomarker of depression in diabetic patients. Along with available tools, it might contribute to timely diagnose of depression and prevent further complications. However, prospective studies are required to be conducted for confirming the causal relationship between BDNF and T2DM.

## 4. Conclusion

BDNF levels were lower in T2DM patients with depression than those without depression. The results suggest that BDNF might be related with the presence of depression in T2DM patients. However, further studies are warranted to elucidate the mechanism by which BDNF may influence depression in T2DM patients. Also, the present study suggests high prevalence of depression in T2DM patients. Therefore, frequent assessment of depression is suggested for early diagnosis of depression thus facilitating active treatment and improving quality of life of T2DM patients.

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## Declaration of competing interest

The authors report no conflicts of interest in this work.

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## References

1 Zhou JX, Li HC, Bai XJ, et al. Functional Val66Met polymorphism of Brain-derived neurotrophic factor in type 2 diabetes with depression in Han Chinese subjects. *Behav Brain Funct*. 2013;9:34.
2 Federation ID. *Diabetes Atlas*. 2020.
3 Islam SM, Ferrari U, Seissler J, et al. Association between depression and diabetes amongst adults in Bangladesh: a hospital based case-control study. *J Glob Health*. 2015;5(2), 020406.
4 Siddiqui S, Jha S, Waghdhare S, et al. Prevalence of depression in patients with type 2 diabetes attending an outpatient clinic in India. *Postgrad Med*. 2014;90(1068):552–556.
5 Nakagawa T, Tsuchida A, Itakura Y, et al. Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. *Diabetes*. 2000;49(3):436–444.
6 Fujinami A, Ohta K, Obayashi H, et al. Serum brain-derived neurotrophic factor in patients with type 2 diabetes mellitus: relationship to glucose metabolism and biomarkers of insulin resistance. *Clin Biochem*. 2008;41(10-11):812–817.
7 He M, Wang J. Decreased serum brain-derived neurotrophic factor in Chinese patients with Type 2 diabetes mellitus. *Acta Biochim Biophys Sin*. 2014;46(5):426–427.
8 Suwa M, Kishimoto H, Nofuji Y, et al. Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. *Metabolism*. 2006;55(7):852–857.
9 Civelek S, Konukoglu D, Erdenen F, et al. Serum neurotrophic factor levels in patients with type 2 diabetes mellitus: relationship to metabolic syndrome components. *Clin Lab*. 2013;59(3-4):369–374.
10 Boyuk B, Degirmencioglu S, Atalay H, et al. Relationship between levels of brain-derived neurotrophic factor and metabolic parameters in patients with type 2 diabetes mellitus. *J Diabetes Res*. 2014;2014, 978143.
11 Zhen YF, Zhang J, Liu XY, et al. Low BDNF is associated with cognitive deficits in patients with type 2 diabetes. *Psychopharmacology (Berl)*. 2013;227(1):93–100.
12 Rashid RR, Fazal A, Khan QU, et al. Comparison of serum brain-derived neurotrophic factor levels in diabetic patients with and without retinopathy. *Cureus*. 2020;12(12), e12028. https://doi.org/10.7759/cureus.12028, 2020 Dec 11.
13 Rozanska O, Uruska A, Zozulinska-Ziolkiewicz D. Brain-derived neurotrophic factor and diabetes, 2020 Jan 28 *Int J Mol Sci*. 2020;21(3):841. https://doi.org/10.3390/ijms21030841. PMID: 32012942; PMCID: PMC7037992.
14 Davarpanah M, Shokri-mashhadi N, Ziaei R. A systematic review and meta-analysis of association between brain-derived neurotrophic factor and type 2 diabetes and glycemic profile. *Sci Rep*. 2021;11, 13773.
15 Lee BH, Kim YK. Reduced platelet BDNF level in patients with major depression. *Prog Neuro Psychopharmacol Biol Psychiatr*. 2009;33:849–853.
16 Cattaneo A, Bocchio-Chiavetto L, Zanardini R, et al. Reduced peripheral brain-derived neurotrophic factor mRNA levels are normalized by antidepressant treatment. *Int J Neuropsychopharmacol*. 2010;13(1):103–108.
17 Wang J, Zhao X, He M. Is BDNF biological link between depression and type 2 diabetes mellitus? *Med Hypotheses*. 2012;79(2):255–258.
18 Fang YJ, Wu TY, Lai JN, Lin CL, Tien N, Lim YP. Association between depression, antidepression medications, and the risk of developing type 2 diabetes mellitus: a nationwide population-based retrospective cohort study in Taiwan 8857230. Jan *Biomed Res Int*. 2021;7, 2021.
19 Derbel CH, Aribi L, Ben Naceur B, et al. Depression in diabetic patients: a comparative study of 100 diabetic patients and 100 controls. *Eur Psychiatr*. 2015;30:724.
20 Icks A, Wittgens C, Haastert B, et al. High depressive symptoms in previously undetected diabetes – 10-year follow-up results of the Heinz nixdorf recall study. *Clin Epidemiol*. 2021;13:429–438.
21 Aschner P, Gagliardino JJ, Ilkova H, et al. High prevalence of depressive symptoms in patients with type 1 and type 2 diabetes in developing countries: results from the International diabetes management practices study. *Diabetes Care*. 2021;44(5):1100–1107.
22 Hussain Hussain A, Wani ZA, Shah H, et al. Depression and diabetes: an experience from Kashmir. *Indian J Psychiatr*. 2020;62:167–171, 2020.
23 Sweileh WM, Abu-Hadeed HM, Al-Jabi, et al. Prevalence of depression among people with type 2 diabetes mellitus: a cross sectional study in Palestine. *BMC Publ Health*. 2014;14:163.

24 Li B, Lang N, Cheng ZF. Serum levels of brain-derived neurotrophic factor Are associated with diabetes risk, complications, and obesity: a cohort study from Chinese patients with type 2 diabetes. *Mol Neurobiol*. 2016;53(8):5492–5499, 2016.
25 Liu W, Han X, Zhou X, et al. Brain derived neurotrophic factor in newly diagnosed diabetes and prediabetes. *Mol Cell Endocrinol*. 2016;429:106–113.
26 Krabbe KS, Nielsen AR, Krogh-Madsen R, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia*. 2007;50(2):431–438.
27 Yamanaka M, Itakura Y, Tsuchida A, et al. Brain-derived neurotrophic factor (BDNF) prevents the development of diabetes in prediabetic mice. *Biomed Res*. 2008;29(3): 147–153, 2008.
28 Ryu JS, Lee YM, Kim YS, et al. Association between BDNF polymorphism and depressive symptoms in patients newly diagnosed with type 2 diabetes mellitus. *Yonsei Med J*. 2021;62(4):359–365.
29 Lu Y, An T, Tian H, et al. Depression with comorbid diabetes: What Evidence exists for treatments Using Traditional Chinese medicine and Natural products? *Front Pharmacol*. 2021;11, 596362.
30 Balogh DB, Molnar A, Hosszu A, et al. Antidepressant effect in diabetes-associated depression: a novel potential of RAAS inhibition. *Psychoneuroendocrinology*. 2020 Aug;118, 104705.
31 Lenart L, Balogh DB, Lenart N, et al. Novel therapeutic potential of angiotensin receptor 1 blockade in a rat model of diabetes-associated depression parallels altered BDNF signalling. *Diabetologia*. 2019;62:1501–1513.
32 Qin L, Chong T, Rodriguez R, Pugazhenthi S. Glucagon-like peptide-1-mediated modulation of inflammatory pathways in the diabetic brain: relevance to Alzheimer's disease. *Curr Alzheimer Res*. 2016;13:1346–1355.