RESEARCH

Metformin Treatment in Adult Patients with Type 2 Diabetes Mellitus and Serum Brain-Derived Neurotrophic Factor

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Abstract: People with diabetes have a much higher risk of impaired cognitive function due to increased vascular aging. Brain-derived neurotrophic factor (BDNF) is one of the most important neurotrophins due to its characteristics, such as protecting neuronal tissue and improving the function of the central nervous system. BDNF level might be related to different factors are age, glucose, drug in Tip II diabetes (T2DM) patients. We have aimed to investigate the association between serum concentrations of BDNF and blood parameters in diabetic patients. Forty-six T2DM patients have been enrolled in this observational study. Serum BDNF, cognitive, hematologic, and biochemical parameters were measured in metformin-taking patients (n=29, Group I) and patients without metformin therapy (n=17, Group II). BDNF, age, gender, blood, and cognitive parameters were statistically insignificant between the groups. BDNF serum level was positively correlated with glucose in all patients (p=0.013). Metformin is the most commonly used anti-diabetic in the treatment of T2DM. Despite many studies indicating the pro-cognitive effects of both metformin and BDNF, our results indicated that there were no significant differences between a specific groups of DM patients suggesting that further studies, including also specific age and disease groups, are needed to clarify the specific role of BDNF and metformin in cognition.

INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in the synaptogenesis of the central nervous system (CNS) [1]. It is therefore involved in the treatment of many neurological diseases[2-4]. In addition to its role in the nervous system, several data have shown that BDNF is also involved in systemic or peripheral inflammatory conditions. One of these important disorders is type 2 diabetes mellitus (T2DM) characterized not only by inflammation but also by several deleterious effects on the central nervous system (CNS)[5,6]. For instance, recent studies have revealed that DM is associated with an increased risk of dementia[7].

Interestingly, even normal glucose levels have been linked to increased cognitive impairment, suggesting a significant association among hyperglycemia, insulin resistance, systemic inflammation, and cognitive impairment[7]. Studies have also indicated that one of the most critical impacts of BDNF on the CNS is its pro-cognitive and anti-depressant effects[8,9]. For instance, several studies of depressive and cognitively impaired subjects have shown impaired BDNF levels[10,11]. However, despite these promising findings, there are still no strong clinical data indicating the role of BDNF in cognitive impairment in DM. The same also applies to metformin, an antidiabetic drug with well-known glucose-lowering properties. Current data indicate that metformin has dual effects on cognition in healthy individuals and those with DM[12].

Furthermore, the question of whether metformin has beneficial effects on dementia development is still controversial[12,13]. Since the vascular endothelium also produces BDNF, while a significant amount is stored in the platelets, it would be interesting to evaluate the plasma levels of BDNF in cognitively impaired DM patients under metformin therapy. To the best of our knowledge, no previous research has to date considered this connection in this specific patient group. However, several studies have indicated altered BDNF levels in patients with DM receiving metformin therapy in line with the duration of DM and metformin use[13]. Additionally, age, sex, and smoking history are important factors that alter BDNF activity[14]. The primary aim of this study was to investigate the correlations among complete blood count, biochemical parameters, and serum BDNF levels in diabetic patients presenting with or without cognitive impairment and receiving or not receiving metformin therapy.

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MATERIALS and METHODS

Forty-six participants with a diagnosis of diabetes in the Department of Internal Medicine enrolled in this cross-sectional study. The study was approved by the Alaaddin Keykubat University, Faculty of Medicine Ethics Committee (14.04.2021/No: 07-10), and informed consent was obtained from all participants.

Patients with T2DM were examined in the Department of Neurology. At baseline assessment, anti-diabetic medications taken by the patients were ascertained from self-reports and physical inspection of pill bottles, boxes, packets, diaries, and other materials for verification. Participants were categorized by metformin usage as non-users and users.

Cognitive status was formally assessed with Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Scores for the 11 components are summed into a total ADAS-cog score. Low total scores indicate better cognitive performance.

All blood samples were taken in fasting condition at 9 a.m. Standard laboratory techniques were used for regular laboratory testing. Serum BDNF concentrations were measured using BDNF Quantikine Immunoassay (R&D Systems, USA).

Statistical analysis

The data were analysed by SPSS version 21 for Windows (SPSS Inc., Chicago, IL, USA). The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean (standard deviation [SD]); non-normal variables were reported as median (%95 Cl, confidence interval). Means of two continuous normally distributed variables were compared by independent samples Student's t test. Mann-Whitney U test and Kruskal-Wallis test were used, respectively, to compare means of 2 and 3 or more groups of variables not normally distributed. The frequencies of categorical variables were compared using Pearson $\chi 2$ or Fisher's exact test, when appropriate. A value of $P < 0.05$ was considered significant.

RESULTS

Demographic and basic clinical characteristics Mean ±SD demographic data, disease, cognitive, biochemical, and hematological parameters for the study population are presented in Table 1.

Among the 46 T2DM patients reporting median age was 52 years (95% CI, 51-56). Twenty-two (48%) were male, and 24 (52%) were female of all patients. The subjects were divided into two groups as metformin taking patients (n=29) and patients without metformin therapy (n=17). There were no differences between these two groups regarding the duration of serum BDNF level, duration of disease, gender, age, cognitive, and blood parameters (Table 2). BDNF level was positively correlated with glucose in all subjects (p=0.013, Pearson's correlation, Table 1). Linear regression was calculated to predict serum BDNF level based on glucose. Glucose significantly predicted depression scores, B= 0.366, t= 2.58, p =0.013. Glucose also explained a significant proportion of variance in BDNF level F (1, 43) = 6.663 with an R2 of 0.134.

Table 1. Demographic and clinical characteristics of the study's patients

Characteristics	Mean (±SD)	Median (minimum-maximum)	95% CI	P (correlation with BDNF)
Age (years)		52 (37-85)	51-56	0.75
Male (n=22)		49.5 (42-85)	47-56	
Female (n=24)		53 (37-74)	51-59	
Duration of disease (days)		1169 (1-7431)	968-2026	0.54
Duration of metformin usage (days)		233.5 (200-3805)	667-1683	0.67
ADAS-Cog score	12.6 (4.8)			0.63
BDNF (ng/Ml)		1.3 (0-42)	2.2-8.5	-
Insulin		16.6 (0-99.5)	17.3-32.3	0.13
HbA1c		7.24 (5.6-14.2)	7.2-8.5	0.19
Glucose		136 (80-313)	131-174	0.013*
Vitamin B12		453 (220-988)	402-524	0.87
TSH		1.15 (0.03-9.26)	0.93-1.87	0.79
TC (mg/dL)		207 (0-316)	186-221	0.98
HDL (mg/dL)	50.9 (9.4)			0.37
LDL (mg/dL)	120.6 (36.9)			0.94
Triglycerides (mg/dL)		163 (45-372)	156-214	0.71
AST		15 (8-60)	15.7-22.6	0.78
ALT		21 (8-100)	18.9-30	0.97
Leukocyte count (×103/µL)	7.5 (2.03)			0.38
Hemoglobin (g/dL)	13.6 (1.5)			0.83
Hematocrit (%)	41.05 (4.35)			0.94
Platelet count (×103/µL)	271.6 (79.9)			0.65
RBC (×103/µL)	4.9 (0.6)			0.24

Normally distributed continuous variables are presented as mean ± SD (standard deviation), whereas variables with non-normally distributed continuous variables are presented as medians with corresponding range and confidence interval. A value of $P < 0.05$ was considered significant.
ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, HDL: High density lipoprotein cholesterol, LDL: Low density lipoprotein cholesterol, RBC: Red blood cells, TC: total cholesterol; TSH: Thyroid-stimulating hormone

Table 2. Patients' characteristics grouped by metformin usage: demographic data

Variables	Group 1 (n=29)	Group 2 (n=17)	p
Age (years) Male (n=22) Female (n=24)	53.45	54.47	0.72
Duration of disease (days)	1666	1075	0.21
ADAS-Cog score	13.17	11.65	0.307
BDNF (ng/Ml)	5.9	4.5	0.66
Insulin	23.69	26.26	0.74
HbA1c	7.39	8.42	0.12
Glucose	151.28	142.94	0.68
Vitamin B12	457.86	474.88	0.75
TSH	1.42	1.39	0.95
TC (mg/dL)	194.13	215.82	0.16
HDL (mg/dL)	51.8	49.05	0.37
LDL (mg/dL)	115.51	125.83	0.33
Triglycerides (mg/dL)	167.89	200.74	0.19
AST	18	19.94	0.53
ALT	23.48	23.41	0.98
Leukocyte count (×103/μL)	7.7	7.29	0.36
Hemoglobin (g/dL)	13.5	13.6	0.91
Hematocrit (%)	41.2	40.7	0.67
Platelet count (×103/μL)	288.24	243.41	0.66
RBC (×103/μL)	5.09	4.8	0.16

Group I: metformin taking patients, Group II: patients without metformin therapy
All the parametric data were compared by independent t tests and the nonparametric data by the Mann-Whitney U test. A value of $P < 0.05$ was considered significant.
ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, HDL: High density lipoprotein cholesterol, LDL: Low density lipoprotein cholesterol, RBC: Red blood cells, TC: total cholesterol; TSH: Thyroid-stimulating hormone

DISCUSSION

Mean age, duration of disease, and blood parameters in the patients with metformin taking and without metformin groups were similar in the present study. Interestingly, however, glucose exhibited a significant correlation with BDNF levels. No differences in cognitive scores were observed between metformin users and non-users with DM. Similarly, no significant differences were determined between these two groups in terms of BDNF levels, although slight elevation of BDNF levels as well as higher cognitive scores, indicating a worse cognition (ADAS >12), were observed in the metformin users. It is difficult to explain these data. However, in the light of recent studies showing the dual effects of metformin on cognition, it may be hypothesized that metformin might be responsible for impaired cognition[13,15]. In that context, metformin has been linked to dementia development in several clinical studies. For instance, a recent Taiwanese trial showed that metformin is associated with dementia development when used for a specific period[16]. The authors of that study reported that metformin increased the risk of Alzheimer's disease (AD) and the development of Parkinson's disease (PD).

However, a study was criticized since it did not measure vitamin B12 levels, an important parameter mediating the cognitive dysfunction in metformin-induced dementia[17]. No differences in vitamin B12 levels were observed in the present study, suggesting that it exerts diverse metformin effects on cognition. Although no significant differences in cognitive scores were observed, a higher rate of dementia diagnosis was found in the metformin group. These studies, including the present research, are in line with several experimental data suggesting an enhancing role of metformin on cognitive dysfunction, possibly related to underlying amyloid-beta aggregation. Metformin has been shown to induce amyloid beta aggregation via activating adenosine monophosphate (AMP)-activated protein kinase (AMPK), a cellular energy sensor, and increased formation of amyloid-β peptides[15]. It was also interesting that BDNF levels increased in cognitively impaired patients using metformin. Although this finding contrasted with the pro-cognitive role of BDNF, a recent study by Suwa et al. revealed higher BDNF concentrations in patients with T2DM than in a healthy control group[5]. Those authors also showed that BDNF was significantly correlated with body mass index (BMI). With serum triglyceride and fasting glucose levels, findings fit well with our positive correlation between BDNF and glucose levels. It may also be hypothesized that decreased peripheral serum BDNF levels may indicate decreased central consumption of BDNF in neurodegenerative conditions. It is therefore not unreasonable to assume that diabetes associated with significant neuroinflammation may result in decreased CNS availability, leading to increased peripheral levels of BDNF. Metformin has also been shown to increased plasma BDNF levels in patients with metabolic syndrome in a recent human study[18]. In the light of all these findings, our findings accord well with recent clinical pre-clinical and clinical data showing the detrimental effect of metformin on cognition associated with increased peripheral BDNF levels. However, since our study sample was relatively small, and due to its cross-sectional design, it is difficult to prove a conclusive cause-effect relationship in which BNDF, cognition and DM are strongly linked together.

Conclusion

In conclusion, despite the above-mentioned limitations, our results provide valuable data. They suggest that further studies, including also specific age and disease groups, are needed to clarify the specific role of BDNF and metformin in cognition.

Conflict of interest

The authors declare that they have no conflict of interest.

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