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Correlation of Doppler examination parameters and brain-derived neurotrophic factor, as a neuromarker, in diabetic patients with polyneuropathy at the stage of late complications

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Abstract---The work was initiated to study correlation between ultrasonic Doppler examination parameters and BDNF, a neuro-marker, in blood of patients with type 2 diabetes mellitus (type 2 DM) and diabetic polyneuropathy (DPN) at the stage of late complications. A comparative prospective study with the participation of 215 patients with type 2 DM, 160 subjects with diabetic polyneuropathy at the stage of late complications were conducted from 2018 to 2021. There is a significant correlation between blood BDNF concentrations and laboratory –instrumental parameters. The correlation between the glycated hemoglobin and Doppler examination in both groups of patients was found, while the correlation with the fasting glycaemia was found insignificant. All the findings can be regarded as the evidence for necessity of timely adequate conservative therapy of chronic wound defects in low extremities of patients with type 2 diabetes mellitus as well as for prevention of recurrences and arrangement of long-term follow-up of patients at high risk of diabetic complications.

Keywords---type 2 diabetes mellitus, diabetic polyneuropathy, Doppler examination, brain-derives.

Introduction

Lately, a lot of works closely focusing on various growth factors with simultaneously produced effects on the vascular and metabolic components of any disorder's pathogenesis have appeared [1,2]. The brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) are among the factors mentioned above. The latest findings demonstrate definite regularities between the more intense activation of these factors at the early stages of diabetic polyneuropathy resulting from the effects of compensation mechanisms, and significant reduction in their generation at the decompensation. [3,4].

Prof. Filimonova T.A. from E.A. Vagner Perm State Medical University, Russian Public Healthcare Ministry, has recently dealt with the role of BDNF in the onset and progression of diabetic foot syndrome (DFS). In 2018, she took out a patent on the method for diagnosis of subclinical study of diabetic polyneuropathy by measurement of the marker in patients with DFS [5,6].

According to Hubert Steigler (2004), diabetic polyneuropathy, macroangiopathy, and a combination of the former and the latter are the main etiological DFS factors. With the ischemia predominated, the progressing macroangiopathy significantly worsens the prognosis resulting in the foot infection and amputation in most cases. External traumas of the foot by inappropriate footwear, foreign bodies and inadequate management in combination with the foot deformation associated with the osteoarthropathy are the triggers. The intense of collagen due to end products of glycosylation, fat tissue loss and edemas are among the pathogenetic factors. [7,8].

The findings from a three-center experimental study conducted in Brazil in 2014 demonstrated that chronic exercise of rats on the treadmill increased plasma brain-derived neurotrophic factor levels, and insulin tolerance in a TrkB-dependent manner

According to Patterson (2015), BDNF may provide a protection for neurons from injuries caused by infections or trauma playing a significant role in many memory processes and memory-related plasticity processes at hippocampal synapses disturbed by IL-1 β irregularity [9].

According to Nils et al. (2015) the brain-derived neurotrophic factor is a driving force behind neuroplasticity essential for maintenance and restoration of the nervous system. However, BDNF facilitates the pain sensitization becoming new therapeutic target. The authors presented an overview of BDNF's sensitizing capacity at each level of the pain pathways. They presented some potential therapeutic approaches ranging from indirect effect on BDNF levels by physical exercises, anti-inflammatory drugs, melatonin and repetitive transcranial magnetic stimulation to more specific targeting of BDNF's receptors and signaling pathways by blocking the proteinase-activated receptors 2-NK- $\kappa\beta$ signaling

pathway, administration of phencyclidine to antagonize NMDA receptors, or block the adenosine A2A [10].

Shafaq et al. (2018) dealt with the microglia derived BDNF playing a key role in chronic pain. Still, the contribution of primary afferent-derived BDNF to chronic pain processing is poorly explored. The authors used Avil-CreERT2 mice deleting BDNF from all peripheral sensory neurons of the adults. According to the authors, BDNF derived from sensory neurons is crucial for facilitation of acute-to-chronic pain transfer. Using a modified Chung model, the authors observed normal transfer of acute to chronic neuropathic pain demonstrating differences in the contribution of BDNF to distinct models of neuropathy [11].

According to Wang et al. (2019), physical training lowered sympathetic activity being beneficial for the prevention and treatment of hypertension, and associated cognitive disorders [12]. Intense BDNF expression in skeletal muscles, heart and brain may contribute to these actions of exercises, but the underlying mechanisms are unclear. After experiments, the authors postulated that hypertension associated with the decreased hippocampal BDNF that can be restored by upregulation of fibronectin type-II domain-containing 5 (FNDC5) caused by physical exercises. Both in normotensive and hypertensive rats only BDNF increased [12].

After a six-center study in China, Miao et al. (2021) presented their data on the pain in the diabetic polyneuropathy. [13]. The authors identified BDNF as inducing mechanical allodynia in rats with diabetic polyneuropathy by activation of transient receptor potential canonical 6 (TRPC6). This can be used in confirmation of possibility to use TRPC6 antagonists as an interesting strategy for management of diabetic polyneuropathy [13].

Materials and Methods

A comparative prospective study with the participation of 215 patients with type 2 DM, 160 subjects with diabetic polyneuropathy at the stage of late complications was conducted at the Department of Suppurative Complications of diabetes mellitus, Ya.Kh. Turakulov Center for the Scientific and Clinical Study of Endocrinology, Uzbekistan Public Healthcare Ministry, from 2018 to 2021. All 160 patients with DPN were subjected to surgery.

For the purposes of the study, the following groups of patients were formed. Fifty five patients and 160 diabetic patients without diabetic neuropathy and with the advanced diabetic neuropathy were included in the 1st and 2nd groups, respectively. The patients of the 2nd group were subdivided into those undergoing amputations of toes, feet and low extremities (n=82) and those undergoing amputations of toes, feet and lower extremities + plastics, the so-called two-stage operations (n=78).

The patients with type 2 diabetes mellitus and DPN met the inclusion criterion. The patients with type I diabetes mellitus, neuro-ischemic diabetic neuropathy and cardiovascular pathology prior to diagnosis of type 2 diabetes mellitus on

maintenance hemodialysis, as well as those with strokes, infarctions and cancer pathology met the exclusion criteria. Clinical-biochemical study including:

- measurement of fasting glycaemia, HbA1C, ALT and AST, bilirubin, prothrombin ratio, creatinine, urea and BDNF in blood,
- functional testing,
- instrumental methods, to name ECG, electroneuromyography and ultrasonic Doppler examination of lower extremities vessels,
- bacteriological analysis of wound exudate ,
- measurement of plantar pressure parameters,
- assessment of life quality ("functional assessment scale of the lower extremities" questionnaire) and methods of statistical data processing were used.

The data were processed by means of Microsoft Excel и STATISTICA.6. Arithmetic mean (M), standard deviation or error of arithmetic mean for all n values (m) was calculated. Inter-group statistical significance was estimated by confidence interval and Student's criterion (p). The differences were significant at $p < 0.05$. The distribution of patients by sex and age can be seen in Table 1 showing predominance of those aged from 60 to 70 both among men and women (129 versus 86 cases).

Table 1.
Distribution of patients by sex and age (WHO, 2017)

Age, years	Men, n (percent)	Women n (percent)
18-44 (young age)	21 (16.3%)	9 (10.5%)
45-59 (middle age)	44 (34.1%)	26(30.2%)
60-74 (old age)	43 (33.3%)	36(41.8%)
≤ 75 (senile age)	21 (16.3%)	15(17.4%)
Total: n = 215	129 (60.0%)	86 (40.0%)

Results and Discussions

The BDNF serum concentrations in patients from the groups under study were comparatively analyzed (Table 2).

Table 2.
Concentrations of BDNF in blood serum of patients under study

Parameter	Controls	1st group	2A group	2B group
BDNF, ng/ml	1.07± 0.64	2.12±0.32	4.74±1.09*	6.74±1.09*

Note: * - significance of differences with the control, where $p < 0.05$)

The serum BDNF concentrations in blood of patients in 2A and 2B groups with diabetic foot syndrome can be seen to be significantly higher than the control ones (Table 2). According to Filimonova (2019), the degrees of plasma BDNF excess are mild, intermediate and high with concentrations ranging from 1.96 to

2.8 ng/ml, from 2.9 to 4.5 ng/ml, and from 4.6 to 7.0 ng/ml, respectively [6].. Thus, mild, intermediate and high BDNF excess could be seen in patients of the 1st group 2A and 2B group, respectively (Table 2). Next, the findings from the ultrasonic Doppler examination of lower extremities vessels were compared in two groups of patients (Table 3) to show turbulent and collateral blood flow in the 1st and 2nd groups of patients, respectively.

Mean blood flow velocity in the femoral artery of patients from the 1st group was 78.1 ± 3.3 cm/s (normal 100 cm/s), while in the tibial artery it was 39.1 ± 4.6 (normal 50 cm/s). The resistance index in the femoral artery was found to be 0.6 ± 0.08 m/s (normal > 1 m/s). The pulsation index in the tibial artery was 1.0 ± 0.07 m/s (normal 1.8 m/s).

Mean blood flow velocity in the femoral artery of patients from 2A group was 46.8 ± 5.3 cm/s (normal 100 cm/s), while in the tibial artery it was 28.5 ± 4.7 (normal 50 cm/s). The resistance index was found to be 0.5 ± 0.02 m/s (normal > 1 m/s). The pulsation index in the tibial artery was 0.6 ± 0.03 m/s (normal 1.8 m/s).

Mean blood flow velocity in the femoral artery of patients from 2B group was 34.7 ± 6.2 cm/s (normal 100 cm/s), while in the tibial artery it was 22.3 ± 3.2 (normal 50 cm/s). The RI in the femoral artery was found to be 0.2 ± 0.05 m/s, while the PI in the tibial artery was 0.4 ± 0.05 m/s (normal 1.8 m/s). Thus, in patients with diabetic polyneuropathy of the advanced stage significant reduction ($p < 0.05$) in all Doppler examination parameters in the low extremities was found, as compared to those with type 2 diabetes mellitus without diabetic polyneuropathy.

Table 3.
Findings from Doppler examination of lower extremities in groups under study
(n, %)

Parameters	Groups of patients, n.			
	1 st 32	2A group 36	2B group 37	Control 20
Blood flow velocity in femoral artery, cm/s	88.1 ± 3.3	$46.8 \pm 5.3^*$	$34.7 \pm 6.2^*$	100 ± 16.2
Blood flow in tibia, cm/s	42.1 ± 4.6	$28.5 \pm 4.7^*$	$22.3 \pm 3.2^*$	50 ± 9.8
Resistance index (RI) in femoral artery, m/s	0.9 ± 0.08	$0.5 \pm 0.02^*$	$0.2 \pm 0.06^*$	1.0 ± 0.9
Pulsation index (PI) in the tibial artery, m/s	1.5 ± 0.07	$0.6 \pm 0.03^*$	$0.4 \pm 0.05^*$	1.8 ± 0.6

Note: * - significance of differences with the control, where $p < 0.05$)

Clinical-laboratory and functional parameters, to name, fasting glycaemia, glycated hemoglobin, blood flow velocity in the femoral and tibial arteries, and some others were chosen to assess the efficacy of BDNF as a neuromarker (Table 4).

Table 4. Correlation (r) of blood BDNF with the laboratory-instrumental parameters as per groups under study

BDNF ng/ml	Fasting glycaemia, mmol/l	HbA1C %	PI in the tibial artery	RI in the femoral artery	Blood flow velocity in the femoral artery	Blood flow velocity in tibia
1 st group	0.35	0.88	0.64	0.69	0.64	0.75
2 nd group	0.35	0.88	0.64	0.69	0.64	0.75

There is a significant correlation between blood BDNF concentrations and laboratory –instrumental parameters (Table 4). The correlation between the glycated hemoglobin and Doppler examination in both groups of patients was found, while the correlation with the fasting glycaemia was found insignificant. All the findings can be regarded as the evidence for necessity of timely adequate conservative therapy of chronic wound defects in low extremities of patients with type 2 diabetes mellitus as well as for prevention of recurrences and arrangement of long-term follow-up of patients at high risk of diabetic complications.

Conclusion

- The excess of BDNF was found mild, intermediate and high in patients of the 1st group, 2A group and 2B group, respectively.
- In patients with diabetic neuropathy of the advanced stage significant reduction ($p<0.05$) in all Doppler examination parameters in the low extremities was found, as compared to those with type 2 diabetes mellitus without diabetic polyneuropathy
- The correlation of BDNF concentrations with the glycated hemoglobin, blood flow velocity in the femoral artery, pulsation index in the tibial artery and resistance index in femoral artery was found.

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