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Original article

Prospects of using resveratrol for cognitive impairment correction in patients with type II diabetes mellitus

Nikita A. Olshevskiy, Sergey M. Glushenko, Lesya N. Gumenyuk, Oksana Y. Gerbali, Elena V. Sarchuk, Leya E. Sorokina

S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia

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Abstract: Our *goal* was to study the effectiveness of resveratrol in correcting cognitive impairments and in normalization of neurotrophin levels in patients with type II diabetes mellitus.
Material and Methods — In a randomized placebo-controlled trial, 100 patients with a verified diagnosis of type II diabetes mellitus took part, who were subsequently placed into two groups: the treatment group of 50 patients taking a polyphenol therapeutic drug in addition to standard therapy, and the comparison group of 50 indivuduals taking a placebo medication in addition to standard therapy. The control group consisted of 30 individuals belonging to the health group I *sensu* RF Ministry of Healthcare. Treatment efficacy was assessed using the Montreal Cognitive Assessment (MoCA) scale. The concentrations of insulin-like growth factor 1 (IFR-1), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) in blood plasma were analyzed before and after treatment completion (10 weeks later).
Results — Before starting treatment, patients exhibited an increase in the level of IFR-1 and a decrease in the content of neurotrophic factors (BDNF and NGF) in their blood plasma. In patients receiving resveratrol in addition to standard treatment, changes in IFR-1, BDNF and NGF in blood plasma were more noticeable relative to the comparison group and approached the values of the control group. According to the MoCA scale, more pronounced dynamics of cognitive functions was observed in patients of the treatment group.
Conclusion — The high efficiency of the polyphenol therapeutic drug resveratrol in the correction of cognitive impairments in patients with type II diabetes mellitus was established. The use of resveratrol promoted the normalization of the levels of IFR-1 and neurotrophic factors in the blood plasma: in the treatment group, a more pronounced statistically significant decrease in the concentration of IFR-1, along with an increase in BDNF and NGF levels, were observed relative to the control group. The clinically significant effect of resveratrol was in the reduction of cognitive deficit symptoms, which was confirmed by the data of dynamic monitoring on the MoCA scale: in treatment group, there was a statistically significant improvements of optical and spatial functions, attention, abstract thinking, and fulfilling delayed reproduction task; in the comparison group, there was a statistically significant improvement solely of completing delayed reproduction task.

Keywords: diabetes mellitus, cognitive disorders, neurotrophic factors, polyphenol therapeutic drug, resveratrol

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Correspondence to Leya E. Sorokina. Address: 4 Academician Vernadsky St., Simferopol 295007, Republic of Crimea, Russia.E-mail: leya.sorokina@mail.ru.

Introduction

Significant relevance of the issue of the cognitive disorders' prevalence directly correlates with the current trend of an increase in the proportion of elderly people in the population, as well as an increase in the number of dysmetabolic ailments, which are currently among the key risk factors for the development of cognitive decline. To date, there is a proven fact of the comorbidity of non-insulin dependent diabetes mellitus with cognitive deficit, the risk of which in type II diabetes mellitus (DM II) patients, according to various sources, increases by 40-90% [1].

It is believed that cognitive impairment in DM II patients is the result of various interacting pathogenetic factors of a metabolic (chronic hyperglycemia and hypoglycemic episodes with activation of oxidative stress, protein glycation, dyslipidemia), vascular (ischemia, leukoaraiosis, lacunar infarctions, endothelial dysfunction), endocrine (hyperinsulinemia and insulin resistance, hyperleptinemia, hypercortisolemia, hyperinsulinemia, etc.) and neurological nature (genetic predisposition; cerebral atrophy, including atrophy of cortical structures; amyloidosis, impaired calcium and catecholamine homeostasis in neurons, depression) [2]. The most common hypotheses determine the role of chronic hyperglycemia, recurrent hypoglycemic episodes, insulin resistance, arterial hypertension, dyslipidemia, micro- and macroangiopathy, and amyloid deposits. However, the mechanisms of the cognitive impairment development in DM II individuals remain largely unclear, which makes it difficult to find effective strategies for their prevention and treatment.

Taking into account the data on the steady growth of dysmetabolic pathologies and cognitive impairments in the

population, the development and implementation of new preventive and therapeutic strategies for initial stages of higher brain functions' impairment becomes especially urgent.

In contemporary scientific literature, the relationship between the effectiveness of individual polyphenol therapeutic drugs and their anti-diabetic effects were noted [3]. For instance, one of the most popular representatives of polyphenol therapeutic drugs found in grapes and red wine is resveratrol, the only registered antiaging drug in the United States for therapeutic and prophylactic use in order to slow down the growth of demographic aging of the population [4].

The use of resveratrol is characterized by a wide range of pharmacological effects; the medication has anti-inflammatory, antitumor, as well as neuro- and cardioprotective effects [5]. There is evidence that resveratrol has therapeutic potential for DM II and its complications [6]. Studies conducted on rodents, as models of diabetes, showed that chronic administration of the drug has reduced hyperglycemia, dyslipidemia and diabetic cardiomyopathy. Also, it has improved glucose tolerance and protected β-cells of the pancreas [3].

The effects of resveratrol indicate its promise as a dietary supplement to alleviate cognitive deficit in diabetic patients. Limiting nutrient intake is known to release neurotrophins, which are involved in counteracting cognitive dysfunction [7]. Resveratrol effectively mimics caloric restriction by inducing the expression of the SIRT1 gene, which, in turn, triggers a cascade of PGC-1α-dependent events that improve mitochondrial functioning and biogenesis, and stimulate the removal of reactive oxygen species [8]. The drug helps to weaken neuroinflammation, which is associated with sirtuin-dependent arrest of the nuclear factor NF-κB and blocking microglial activation [9]. Possessing antioxidant activity, resveratrol prevents mitochondrial dysfunction, caused by iron, *via* inhibiting GSK-3β gene and reducing lipoprotein peroxidation [10]. Additionally, the use of resveratrol reduces the negative effect of cerebral vascular ischemia by inhibiting the proinflammatory cytokine – IL-1β, activation of NLRP3 inflammasomes, reducing oxidative stress, and inhibiting apoptosis [11]. The research by Witte A.V. et al. demonstrated that systematic use of resveratrol increased cerebral circulation [12]. Studies by other authors indicated that administration of this therapeutic drug modulated brain function in healthy elderly people, improving glucose metabolism and vasorelaxation by stimulating the synthesis of eNOS and nitric oxide (NO). The above data confirmed that resveratrol had significant potential as a neuroprotective agent [13].

Thus, the goal of our study was to investigate an effectiveness of resveratrol in correction of cognitive impairment and normalization of neurotrophin levels in DM II patients**.**

Materials and Methods

Study design

The study involved 130 people 35 to 45 years of age, 100 of them with a verified (according to the ICD-10 classification criteria) diagnosis of DM II, who were hospitalized into Division of Endocrinology at N.N. Semashko Republic of Crimea Clinical Hospital (Simferopol). Of those, 70 were men (62.2%), while 60 were women (37.8%). The average age of the study subjects was 38.2±2.4 years.

According to the design of a randomized placebo-controlled study, patients with DM II, after medical examination, were randomly divided into two groups: the treatment group (TG) (n=50) with individuals, taking a polyphenol drug in addition to standard therapy, and the comparison group (CG) (n=50), taking a placebo medication in addition to standard therapy. The groups were comparable in terms of the main indicators of their demographic profiles, as well as duration and severity of the illness.

The control group (CL) included 30 persons 35 to 45 years old (average age 39.2±1.9 years) belonging to the health group I *sensu* classification by the Russian Federation Ministry of Healthcare: people who have not been diagnosed with chronic non-infectious diseases, without risk factors for developing such diseases, and not in need of a health screening for other diseases or conditions.

Our study was carried out in accordance with a GCP (Good Clinical Practice) international quality standard and the World Medical Association Declaration of Helsinki. It was approved by the Ethics Committee of V.I. Vernadsky Crimean Federal University, S.I. Georgievsky Medical Academy, Simferopol, Russia. Written informed consent was obtained from all study participants prior to their enrollment.

Compliance criteria

The inclusion of patients in the study was carried out if the following criteria have been met: 1) women and men 35 to 45 years of age; 2) a verified diagnosis of DM II for over 12 months; 3) confirmed mild or moderate cognitive impairments: 20–26 points on the Montreal Cognitive Assessment scale (MoCA); 4) written informed consent.

Exclusion criteria for our study subjects: 1) hypoglycemic and/or ketoacidotic coma in the last three months prior to the study; 2) hypothyroidism; 3) current severe or decompensated concomitant somatic disorders; 4) history of neuroinfections, acute cerebrovascular accident or myocardial infarction during six months preceding the study; 5) conditions after severe craniocerebral trauma and surgeries; 6) stage III hypertension; 7) angina pectoris of the functional class IV, according to the New York Heart Association (NYHA) Functional Classification, i.e. inability to carry out any physical activity without symptoms of heart failure, or such symptoms at rest; 8) hematological and oncological diseases; 9) ongoing intake of psychotropic medications.

Treatment tactics

Standard glucose-lowering therapy was conducted in accordance with the algorithm of specialized medical care for the patients with diabetes mellitus [14].

Polyphenol correction of cognitive impairments was carried out with resveratrol (*Natural Resveratrol* brand, Now Foods company, USA, registration certificate of the Russian Federation Ministry of Health No. RU. 77.99.01.003.E.002745.02.15 of 06.01.2011). The Natural Resveratrol drug was taken *per os*, 1 capsule 3 times a day, with meals, for 10 weeks.

Screening methodology

In the course of our study, we used the clinical anamnestic method, enzyme-linked immunosorbent assay test (ELISA) and neuropsychological testing. By means of ELISA, the content of the

following biochemical markers in blood plasma was determined: insulin-like growth factor-I (IFR-I), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) *via* using kits from *Cusabio Biotech Co., Ltd*, USA (official distributor in the Russian Federation: *Laboratory Diagnostics*, license No. 42/2000-0695-0886 of the Russian Federation Ministry of Healthcare).

As part of neuropsychological testing, a screening assessment of cognitive impairment was performed, using the Montreal Cognitive Assessment (MoCA) scale [15]. The maximum number of points on this scale is 30, the norm is 26 and above.

Patients with DM II were examined twice: initially (when seeking help) and after 10 weeks of therapy. The examination of CL subjects was carried out just once.

Statistical analysis

For statistical data processing, we used Statistica 10.0 software and Medstat program. Data normality confirmed their normal distribution; hence, parametric statistical comparison mthods were employed. For quantitative data, arithmetic means, standard deviations and standard errors were used. In comparative analysis, the statistical significances of the differences in sample means for every indicator were determined *via* one-sample Student's t-test. Differences among sample means were considered significant at $p<0.05$.

Results

In the course of studying concentrations of biochemical blood markers in DM II patients prior to the treatment, we noted the dysfunction of IGF-I and neurotrophic factors in the blood plasma.

Before the start of therapy in DM II patients, a significant 1.3 times increase of IFR-I content in the blood plasma was recorded, compared with the CL (p=0.048). A decrease in IFR-I content relative to its initial level, more pronounced in TG, was observed against the background of therapeutic treatment in the studied groups: its concentration declined 1.8-fold vs. CG (p=0.002) and virtually approached the values of the CL (p>0.05).

An average background level (i.e. before the treatment) of BDNF in the blood plasma of DM II patients was significantly lower than in the CL subjects – by 1.7 times (p=0.006). Against the background of the therapy in TG, there was some positive dynamics in the studied neurotrophic factor: BDNF content increased 1.6 times relative to the initial values (p=0.002), significantly exceeding CG level (p=0.015), whereas it was not statistically different from CL (p>0.05). While BDNF content in the CG tended to increase, there were, however, no significant differences found between its initial value and after standard therapy (p>0.05).

Mean background NGF level (i.e. before treatment) in the blood plasma of DM II patients was also significantly lower, compared with the CL subjects – by 2.5 times (p<0.001). Against the background of the therapy, an increase in NGF level was recorded in the TG patients. It should be noted that, in TG subjects, the changes were more pronounced than in CG patients – by 1.6 times (p=0.004), and approached those in CL. The dynamics of IFR-1 and neurotrophic factors during the therapy is presented in *Table* 1.

In the course of dynamic monitoring on the MoCA scale: a statistically significant improvement in visuospatial functions (p=0.001), sustained attention (p=0.001), abstract reasoning (p=0.047), and memory recall (p=0.048) was observed in TG subjects. In the CG, statistically significant differences were documented only for memory recall indicator (p=0.048) (*Table* 2).

Discussion

Our results have shown that the use of polyphenol therapy is quite promising for the treatment of diabetic encephalopathy, in particular, cognitive deficit. The latter often complicates the course of DM II.

With regard to the issue of IFR-I content in DM II patients, the peptide concentration in the blood plasma, prior to the treatment, in TG patients was statistically significantly higher than the control values. Considering that the state of insulin resistance is accompanied by compensatory hyperinsulinemia, an IFR-I increase in the blood plasma in DM II patients may be a consequence of the stimulating effect of insulin on the synthesis of somatomedin C in the liver. Our results are consistent with the published data, showing that, in non-insulin-dependent diabetes mellitus patients, there is a relative increase in the IFR-I concentration, not associated pathogenetically with a growth of insulin resistance. Such increase is a marker of the latter condition [16].

Table 1. Dynamics of changes in the concentration of insulin-like growth factor and neurotrophic factors during therapy

Indicators	*Control group (CL) (n=30)*	*Treatment group (TG) Before therapy (n=50)*	*Comparison group (CG) Before therapy (n=50)*	*Treatment group (TG) After therapy (n=50)*	*Comparison group (CG) After therapy (n=50)*
IFR-1, ng/ml	192.1±33.1	254.5±76.2*	258.3±74.8*	202.7±31.5•	243.1±36.3*#
BDNF, ng/ml	27.8± 2.6	15.2±3.1**	16.1±3.4**	23.6±3.2	18.4±2.9*#
NGF, ng/ml	0.468 ± 0.02	0.199 ± 0.02**	0.172 ± 0.01**	0.337 ± 0.06*	0.217 ± 0.04

* – p<0.05 in relation to the CL; ** – p<0.01 in relation to the CL; • – p<0.05 in relation to the initial value; # – p<0.05 in relation to the indicators of TG and CG.

Table 2. Dynamics of cognitive functions according to the MoCA scale in patients with type II diabetes mellitus during therapy

Indicators	*Treatment group (TG) Before therapy (n=50)*	*Comparison group (CG) Before therapy (n=50)*	*Treatment group (TG) After therapy (n=50)*	*Comparison group (CG) After therapy (n=50)*
Visuospatial functions	4.0 [3.0; 4.0]	4.0 [3.0; 4.0]	4.0 [4.0; 5.0] ••*	4.0 [3.0; 4.0]
Naming task	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]
Sustained attention task	3.0 [2.0; 4.0]	3.0 [2.0;4.0]	5.0 [4.0; 6.0] ••*	3.0 [2.0; 4.0]
Speech assessment	3.0 [2.0;3.0]	3.0 [2.0;3.0]	3 [3.0; 3.0]	3.0 [2.0; 3.0]
Abstract reasoning	1.0 [1.0; 2.0]	1.0 [1.0; 2.0]	2.0 [2.0; 2.0] •	1.0 [1.0; 2.0]
Memory recall task	2.0 [2.0; 2.0]	2.0 [2.0; 2.0]	4.0 [4.0; 4.0] •	3.0 [3.0; 3.0] •
Orientation to time and place	6.0 [6.0; 6.0]	6.0 [6.0; 6.0]	6.0 [6.0; 6.0]	6.0 [6.0; 6.0]
Total score	22.0 [20.0; 25.0]	22.0[20.0; 25.0]	26.0 [26.0; 28.0] •	24.0 [21.0; 26.0]

• – p<0.05 in relation to the initial value; •• – p<0.01 in relation to the initial value; * – p<0.05 in relation to the indicators of TG and CG.

Considering that an imbalance of neurotrophic factors plays a crucial role in the development of any neurodegenerative conditions, the fact of a decrease in the concentrations of BDNF and NGF in DM II patients is of particular interest. Experimental and clinical studies have shown that the main consequence of hyperglycemic events in diabetes is the accumulation of free oxygen radicals. These, interacting with the plasma membranes of cells, contribute to lipid peroxidation, fragmentation of DNA molecules and a decrease in the level of intracellular ATP [17, 18]. Increased oxidative and nitrosative stress reduces the activity of natural factors of endogenous antioxidant defense, which leads to increased sensitivity and death of β-cells in the pancreas. Such proinflammatory events reduce the activity of proteases and contribute to a shift in the proNGF/NGF and proBDNF/BDNF ratios towards the prevalence of precursors, which in turn explains the deficiency of mature neurotrophins in the systemic circulation [19]. Considering that a decrease in the content of neurotrophins, BDNF and NGF, is considered a reliable biomarker of neuronal dysfunction, associated with cognitive impairment, the statistically significant increase in the concentrations of these neutrophic factors in TG patients, observed in our study, may be regarded as a confirmation of a decrease in the severity of cognitive deficit. These results support the literature data, concerning the finding that systemic stabilization of BDNF and NGF concentrations contributes to reduction of cognitive symptoms, both directly in the structure of organic pathology and in various diseases of dysmetabolic genesis [20].

It is important to emphasize that obtained data demonstrated a more pronounced positive tendency towards the normalization of neurotrophic factors' concentrations in patients who received complex treatment of the *standard therapy + resveratrol* type, relative to the examined CG subjects. This finding is consistent with the results of studies by other authors, who proved the positive effect of polyphenols on normalizing cognitive status in conditions of various metabolic disorders [21].

Besides, the correction effectiveness of cognitive impairments in DM II patients, taking a polyphenol therapeutic drug in addition to standard therapy, was confirmed by the dynamic monitoring results *sensu* the MoCA scale.

Induced by diabetes mellitus, chronic ischemia, accompanied by the development of a cascade of biochemical reactions, underlies tissue damage in the brain. Considering that nerve cells are especially sensitive to depletion of energy resources and oxidative stress, traditional drug therapy, aimed at improving the blood supply to the brain, is not always pathogenetically justified in conditions of cognitive deficit development of dysmetabolic genesis [22-24]. Since the mechanism, preventing and eliminating the consequences of damage, caused by free oxygen radicals, specifically the endogenous antioxidant system contained in cells in low concentrations, cannot cope with the pathological process, the supply of antioxidants from the outside is required.

Thus, using polyphenol medication – resveratrol in the complex therapy of DM II, due to membrane stabilization, formation of interconnected membrane complexes of neurons, and activation of synaptic processes, has a pronounced neuroprotective effect and improves the cognitive abilities of patients.

Conclusion

In patients with DM II, in the presence of cognitive impairments, we observed an increase in IFR-I level, along with a decrease in the content of neurotrophic factors (BDNF and NGF), in their blood plasma.

Using a polyphenol therapeutic drug for the correction of cognitive impairments in DM II patients contributed to normalizing the content of IFR-I and neurotrophic factors in their blood plasma: in the TG, we established a more pronounced statistically significant decrease in the concentration of IFR-I, BDNF and NGF, compared with the CG.

The clinically significant effect of resveratrol was manifested in the reduction of the cognitive deficit symptoms, which was confirmed by the data of dynamic monitoring on the MoCA scale: in the TG, there was a statistically significant improvement in visuospatial functions, sustained attention, abstract reasoning and fulfilling the memory recall task, whereas in the CG, solely memory recall.

Limitations

The results of this study should be interpreted taking into account some limitations. First, there is a relatively small sample size of patients. Another limitation is the fact that age at onset of diabetes was not considered among eligibility criteria. In addition, the collected data cannot be extrapolated to patients treated on an outpatient basis and beyond the selected age limits. The limitations of currently available screening tools for cognitive impairment should also be considered. Most screening tests set limits on outcomes that do not account for, or account just partially for, the effects of age and educational attainment, while these parameters are important predictors of cognitive function. Besides, some authors have questioned the diagnostic accuracy of the globally used MoCA test to differentiate between cognitive decline and the development of mild cognitive impairment.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Conflict of interests

We declare no conflict of interest.

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Authors:
Nikita A. Olshevskiy – Senior Year Student, S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia. https://orcid.org/0000-0002-9290-3260.
Sergey M. Glushenko – senior year student, S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia. http://orcid.org/0000-0001-5148-9350.
Lesya N. Gumenyuk – MD, DSc, Professor, School of Medical Personnel Training and Supplementary Vocational Education; Department of Psychiatry, Narcology, Psychotherapy with the Course in General and Medical Psychology, S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia.
Oksana Y. Gerbali – MD, Associate Professor, Department of Surgery No. 1, School of Medicine, S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia. http://orcid.org/0000-0001-7601-6226.
Elena V. Sarchuk – MD, PhD, Associate Professor, Department of General Hygiene with Ecology, S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia. http://orcid.org/0000-0001-9362-3626**.**
Leya E. Sorokina – Senior Year Student, S.I. Georgievsky Medical Academy, Vernadsky Crimea Federal University, Simferopol, Russia. http://orcid.org/0000-0002-1862-6816.