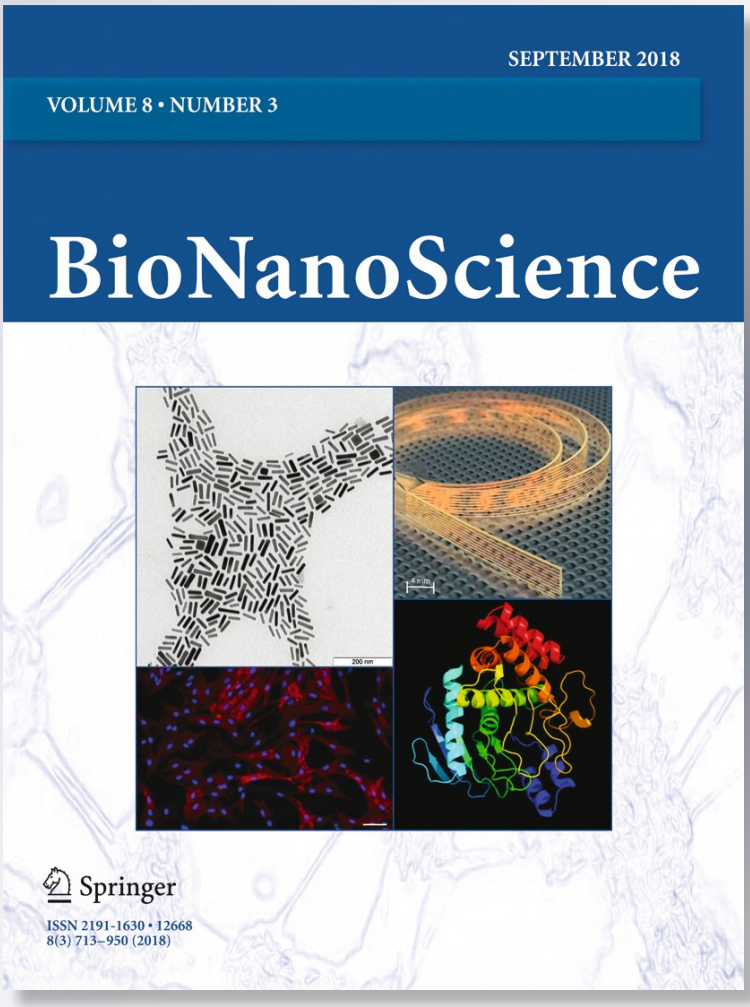
Influence of Standardized Extract Ginkgo biloba *EGb761® Towards Quality of Life Indicators in Patients with Diabetes Mellitus Type 2*

Radiy Esin, Oleg Esin & Ilshat Khayrullin

BioNanoScience

ISSN 2191-1630
Volume 8
Number 3

BioNanoSci. (2018) 8:916-923
DOI 10.1007/s12668-018-0550-3



Springer

BioNanoScience (2018) 8:916–923
https://doi.org/10.1007/s12668-018-0550-3

Influence of Standardized Extract *Ginkgo biloba* EGb761® Towards Quality of Life Indicators in Patients with Diabetes Mellitus Type 2

Radiy Esin [1,2,3,4] · Oleg Esin [1,3,4] · Ilshat Khayrullin [1]

Published online: 25 July 2018

Abstract
Cognitive impairment in patients with type 2 diabetes mellitus (DM-2) currently attracts a lot of attention due to their impact on quality of life and the effectiveness of treatment. The aim of research is to find the most effective medication which influences the cognitive functions positively. The research included 120 patients with average age of 61.22 ± 8.6 and average DM-2 duration of 10.84 ± 8.2 years. Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA test), Trail Making Test (TMT), Parts A and B, Hospital Anxiety and Depression Scale (HADS), and The Short Form-36 (SF-36) were used. It was revealed that patients with DM type 2 had cognitive dysfunction generally presented by mild cognitive impairment. Patients with DM-2 have an early manifestation of cognitive impairment. After the initial estimation of indicators, all the patients were taking standardized extract *Ginkgo biloba* (EGb 761®) in the dose 240 mg a day for 6 months. Estimation of all the indicators after 3 and 6 months of treatment showed significant cognitive improvement. By matching the available experimental and clinical data, we can conclude that in the setting of DM-2 EGb 761®, by producing a positive effect towards various factors which results from insulin resistance of the brain, improves functions of the brain, which manifests in improvement of main QoL indicators in DM-2.

Keywords Diabetes mellitus type 2 · Cognitive decline · EGb 761 · Quality of life · Neurocognitive tests

1 Introduction

Cognitive impairment in patients with type 2 diabetes mellitus (DM-2) currently attracts a lot of attention due to their impact on quality of life and the effectiveness of treatment. It is a problem of great importance to find the most effective medication which influences the cognitive functions positively.

✉ Radiy Esin
radyesin@gmail.com

[1] Laboratory of Clinical Linguistics, Kazan Federal University, 2 Tatarstan str., Kazan, Russia 420008

[2] Department of Neurology and Manual Therapy, Kazan State Medical Academy, 11 Mushtari str., Kazan, Russia 4200124

[3] Department of Fundamental Basis of Clinical Medicine, Kazan Federal University, 56 K.Marks str., Kazan, Russia 420012

[4] Department of Russian Language and Applied Linguistics, Kazan Federal University, 2 Tatarstan str., Kazan, Russia 420008

Diabetes mellitus is defined by the WHO and UN as a non-infectious disease with epidemic prevalence rate [1]. The number of patients suffering from DM increases every year. There is no generally accepted definition of QoL. Usually, it is explained as individual's ability to act in accordance with own public position and to enjoy life. WHO defines QoL as individuals' perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. QoL evaluation shows different changes in patients' condition predicated by their health, both physical and psychological. Criteria of QoL are divided into two groups: objective and subjective. Objective criteria are occupational rehabilitation and physical activity; subjective criteria are emotional status, well-being, and life satisfaction [2].

QoL in patients with insufficient glycemic index control has statistically lower levels comparing with those with constant glycemic index [3, 4].

The objective of this study is to determine if standardized extract *Ginkgo biloba* (EGb 761®) improves the QoL indicators in patients with DM type 2. This

Table 1 Assessment tools

Cognitive functions	Baseline neurocognitive tests	Mini Mental State Examination (MMSE) [5]
		Montreal Cognitive Assessment (MoCA test) [6]
		Trail Making Test, Parts A and B [7]
Depression and anxiety	Hospital Anxiety and Depression Scale (HADS) [8]	
QoL	The Short Form-36 (SF-36) [9]	

objective required (a) evaluation of the QoL in patients with DM type 2 and (b) revealing the affecting factors.

2 Materials and Methods

The research included 120 patients (70 females and 50 males) with average age of 61.22 ± 8.6 and average DM-2 duration of 10.84 ± 8.2 years.

Inclusion criteria were as follows:

- Age of 40–75, presence of diabetes mellitus type 2;
- Absence of complaints connected with memory problems;
- Absence of complaints connected with disorders of sensitivity in extremities, pain and diminution of strength in extremities;
- Signed informed consent of the patient for participation in the study.

Exclusion criteria were as follows:

- Old apoplectic attack and/or myocardial infarction;
- Heart rhythm disorder (atrial fibrillation);
- Presence of hematological, oncological, serious infectious diseases;
- State after severe traumatic brain injuries and surgeries;
- Refusal to sign the Informed Consent of the patient for participation in the study;
- Presence of other endocrine diseases;
- Retinopathy: pre- and proliferative phase;
- Glomerular filtration rate below 60 ml/min/1.73 m^2.

The assessment included evaluating the patients' cognitive functions, anxiety, depression, and QoL as shown in Table 1.

Statistical data processing was conducted using Statistica 10.0 package. The methods of descriptive statistics and the estimation of distribution normality were used according to the Shapiro–Wilk test. Spearman's approach was used for correlation estimation as some data had abnormal distribution. The comparison between groups was conducted using the Mann–Whitney *U* test. The results are represented as the average values and medians with quartile indication.

After the initial estimation of indicators, all the patients were taking standardized extract *Ginkgo biloba* (EGb 761®) in the dose 240 mg a day for 6 months. The repeated estimation of all the indicators was performed after 3 and 6 months.

3 Results

It was revealed that patients with DM-2 type 2 had cognitive dysfunction: 82.5% of patients had cognitive decline according to MMSE and 80.6% of patients—according to the MoCA test—were mainly due to decreased attention, short-term memory and speed of thinking. In 80% of them, there was registered a moderate cognitive decline, and 20% had a severe cognitive decline at the border with dementia. Average results of MMSE are 27 points (26; 27), MoCA 24 (22; 26) points, TMT A 53 (38; 67) s, and TMT B 120 (82; 176) s.

QoL indexes in patients with DM type 2 are significantly lower in comparison with general population and normal scores as shown in Figs. 1 and 2.

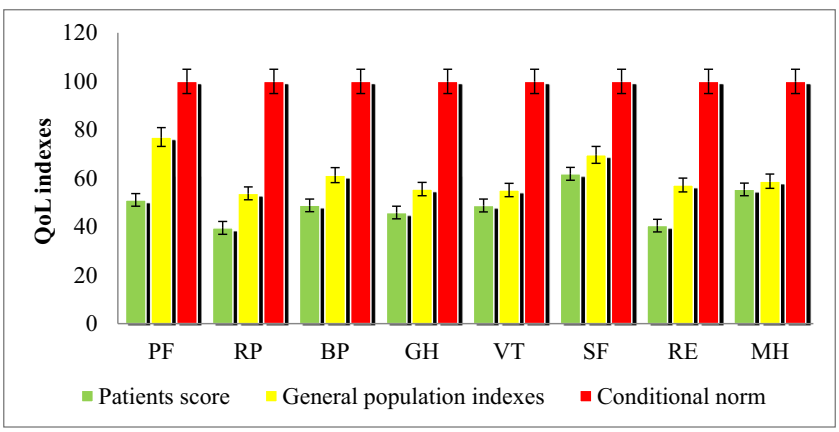


Fig. 1 The QoL comparison in general population and conditional normal indexes. Average QoL indexes in patients with DM type 2, general population indexes and conditional normal indexes, $p < 0.001$. PF physical functioning, RP role-physical functioning, BP bodily pain, GH general health, VT vitality, SF social functioning, RE role-emotional, MH mental health. $p < 0.01$

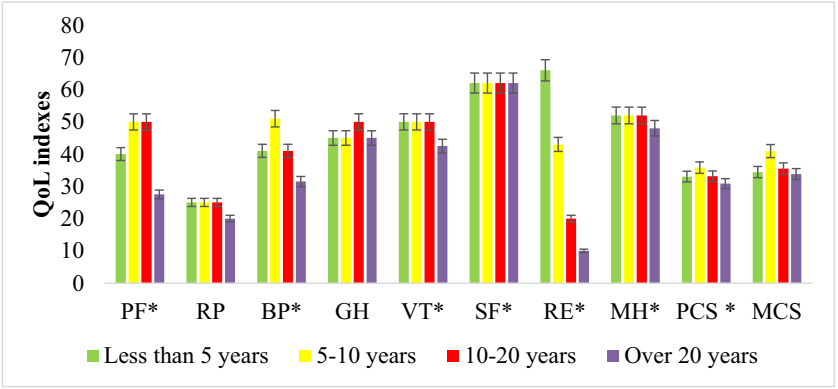


Fig. 2 Dynamics of QoL indexes respectively to disease duration. Correlation of QoL indexes with disease duration, $*p < 0.001$. PF physical functioning, RP role-physical functioning, BP bodily pain, GH general health, VT vitality, SF social functioning, RE role-emotional, MH mental health, PCS physical component summary, MCS mental component summary.

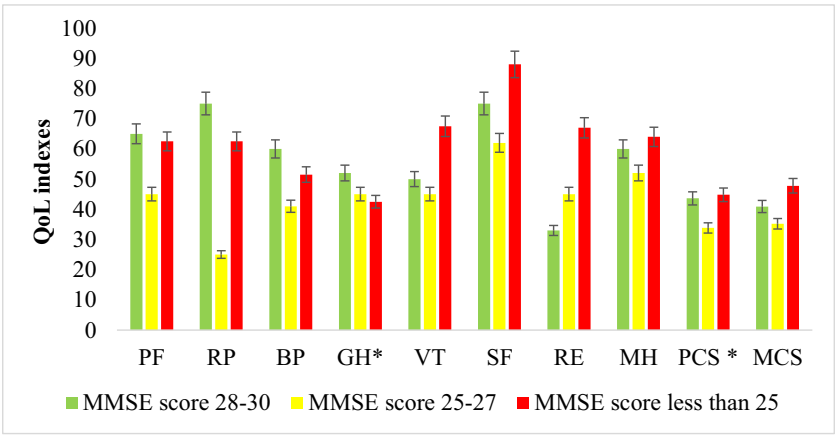


Fig. 3 Correlation of *QOL indexes* with *cognitive decline* (MMSE evaluation), $*p < 0.01$

Figure 1 represents the QoL comparison in general population and conditional normal indexes.

Patients with DM-2 have an early manifestation of cognitive impairment, which can affect both the QoL and the correlation with disease duration as shown in Figs. 3 and 4.

The dynamics of results is statistically significant and has a positive correlation. The QoL evaluation in relation to increase of TMT performance time is presented in Figs. 5 and 6.

The results of emotional condition influence on the QoL evaluation are presented in Figs. 7 and 8.

The research revealed negative correlation of QoL with anxiety and depression. As anxiety and depression indexes increase, the QoL score decreases—this tendency is observed for all QoL factors.

Estimation of all the indicators after 3 and 6 months of treatment with (EGb 761®) 240 mg a day showed significant improvement of the MMSE and MoCA indicators. Further,

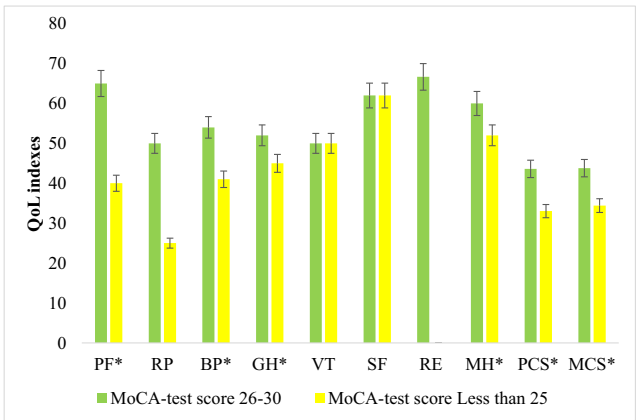


Fig. 4 Correlation of QoL indexes with cognitive decline (MoCA test assessment), $*p < 0.01$

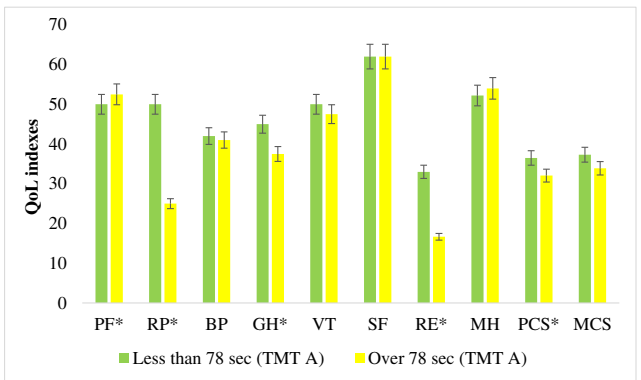


Fig. 5 Correlation of QoL indexes with bradyphrenia severity (TMT part A), $*p < 0.01$

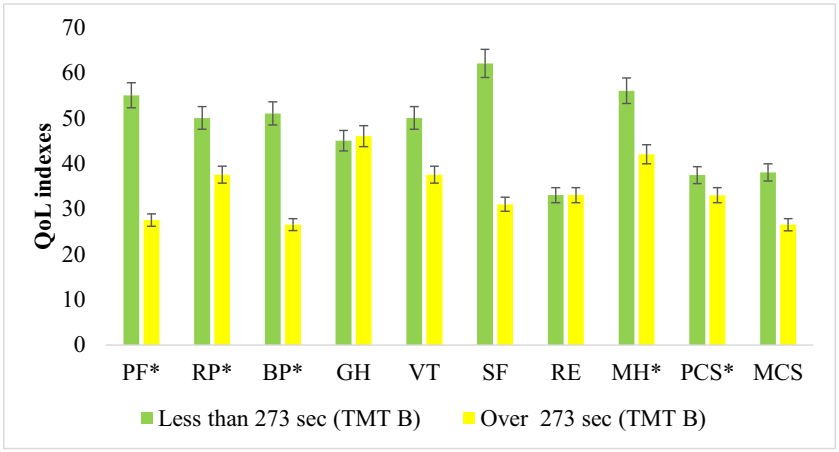


Fig. 6 Correlation of QoL indexes with bradyphrenia severity (TMT part B) *$p < 0.01$

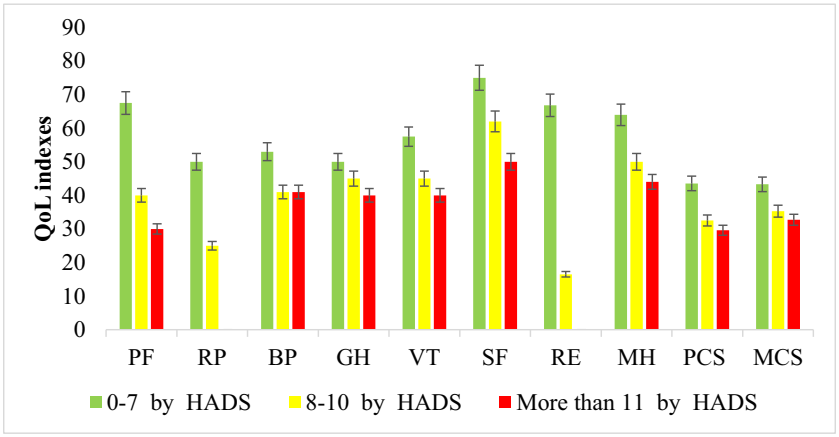


Fig. 7 Correlation of the QoL with depression severity (HADS assessment), $p < 0.01$ in each QoL indicators

this improvement of indicators continued until at least 6 months as score comparison after 3 and 6 months showed statistical significance of differences as shown in Table 2.

During treatment, decrease of average time of TMT-A performance and increase of average time of TMT-B take place as shown in Fig. 9. This phenomenon is due to the fact that the patients who refused (could not) to perform the test (their data was not included in the report) could perform it with a higher time consumption after 3 and 6 months. The average result for such patients amounted to above 273 s (the norm is 273 s). It should be noted that there were no statistically significant changes in time of TMT performance. The statistics enable to state that bradyphrenia had not changed significantly over the 6 months in this number of patients.

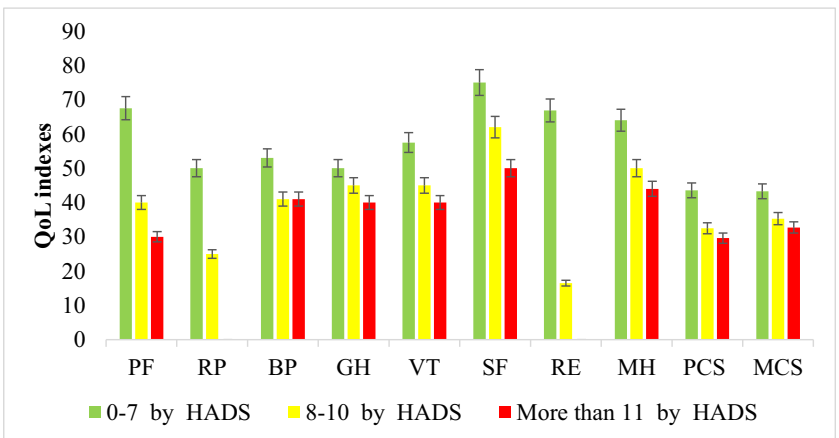


Fig. 8 Correlation of the QoL with anxiety severity (HADS assessment), $p < 0.01$ in each QoL indicators

Table 2 Comparison of the results of MMSE and MoCA indicators with those after 3 and 6 months of treatment

Test	Before treatment	After 3 months of treatment	After 6 months of treatment
MMSE	26 (25; 27)	27 (26; 27), $p^* = 0.04$	28 (27; 28); $p^* = 0.03$, $p^{**} = 0.03$
MoCA	23 (21; 25)	24 (23; 25), $p^* = 0.03$	25 (25; 26); $p^* = 0.01$, $p^{**} = 0.03$

p^*—significance of differences compared to the initial data (before treatment)

p^{**}—significance of differences when indicators are compared after 3 and 6 months of treatment

The anxiety and depression score (HADS) has shown the statistically significant improvement trend when the initial data was compared to the data after 3 and 6 months, but further improvement of the indicators (longer than 3 months) was not revealed as shown in Table 3.

Integrative quality of life have shown improvement both when the results after 3 and 6 months were compared to the initial data and when the data was compared after 3 and 6 months; therefore, the positive changes continued as shown in Table 4. Indicators of pain evaluation did not achieve the statistically significant differences. It should be noted that patients with neuropathic pain were not included in the study. The described pain is musculoskeletal pain and headache.

4 Discussion

Our study has shown that EGb 761® produces positive effect towards various QoL indicators in DM type 2.

Experimental models of DM-2 have repeatedly demonstrated the protective effect of EGb 761® manifested in decrease of clinical presentations of algesic polyneuropathy, deceleration of development of atherosclerosis in model of DM-2 [10], decrease in manifestation of diabetic enteropathy due to influence towards the autonomic nervous system [11], and decrease in myocardial injury caused by diabetic damage of vegetative fibers, which characterizes it as a highly effective adjuvant for treatment of vegetative cardiovascular autonomous neuropathy [12]. EGb 761® produces the nephroprotective effect in the setting of diabetic and hypoxic nephropathy [13].

Intermittent hyperglycemia (IH) is one of the main signs of DM-2, which has the principal importance for development of cardiovascular complications that occur, among other things, due to oxidative stress resulting in endothelial dysfunction. A study performed on endothelial cells of the umbilical vein subjected to IH has shown that IH causes oxidative stress and oxidative damage of DNA of endothelial cells [14]. This damage can be inhibited by EGb 761® (25–100 μg/ml) with the dose-dependent effect. Authors believe that the study results can be used as a novel approach to endothelial protection in IH.

It is commonly known that Alzheimer's disease (AD) is characterized by extracellular accumulation of amyloid-beta and microglial inflammation. The anti-inflammatory effect and mechanisms of the EGb 761® effect were studied in transgenic TgCRND8 mice with hyperexpression of amyloid precursor protein. The product was given with food during 2–5 months; blood plasma concentration of the product was maintained similar to that in persons administering the product in the dose of 240 mg/day. A 5-month treatment course significantly improved cognitive functions of the mice determined by the Barnes maze test, reduced losses of synaptic

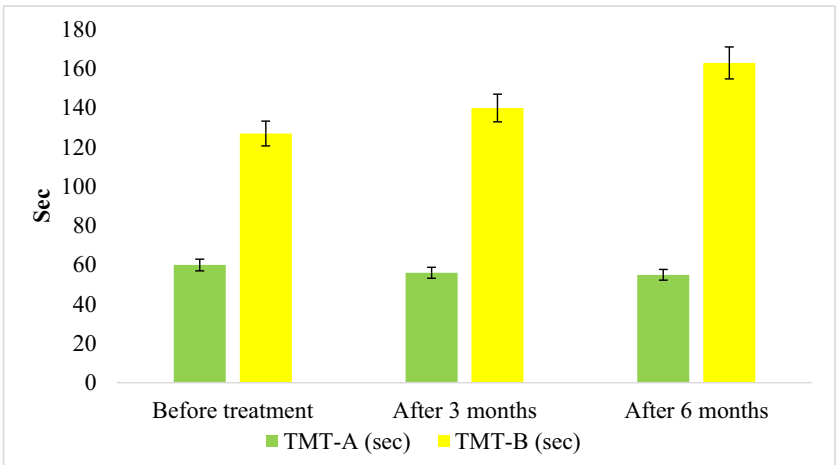


Fig. 9 Time for TMT performance before and during treatment

Table 3 Dynamics of depression and anxiety indicators (HADS score) during treatment

Test	Before treatment	After 3 months of treatment	After 6 months of treatment
Depression	7 (4; 10)	6.5 (4; 9), $p^* = 0.01$	6.5 (4; 8); $p^* = 0.01$, $p^{**} = 0.14$
Anxiety	7 (5; 11)	7 (4; 10), $p^* = 0.01$	6 (4; 10); $p^* = 0.03$, $p^{**} = 0.11$

p^*—significance of differences compared to the initial data (before treatment)

p^{**}—significance of differences when indicators are compared after 3 and 6 months of treatment

proteins (PSD-95, Munc18-1, and SNAP25), and inhibited microglial inflammation. Also, secretion of microglia pro-inflammatory cytokines by the cells was reduced (TNF-α and IL-1β and activation of caspase-1), and microglial autophagy was inhibited. Additionally, it was discovered that EGb 761® decreased amyloidogenesis through inhibition of beta-secretase and aggregation of amyloid-beta peptide [15]. Authors of another study confirm that catechins and procyanidins, which are one of major active components of EGb 761®, possess the ability to inhibit aggregation of A-beta amyloid protein and destabilize the formed fibrillae. A study of isolated components of EGb 761® has shown that flavonoids 1, 3, and 4 possess the highest activity in inhibiting aggregation of A-beta amyloid [16].

Currently, pathogenesis of cognitive disorders in the setting of DM-2 and AD is viewed from the perspective of insulin resistance of brain [17]. Common links of pathogenesis of DM-2 and AD enable to call AD the type 3 diabetes mellitus [18]. It is known that insulin regulates the peripheral homeostasis of glucose. However, it has been established that insulin signaling plays an important role in various sectors of brain and ensures regulation of many functions, such as development of neurons, glucose regulation, behavioral reactions, bodyweight regulation, and cognitive processes, such as attention, executive functions, learning, and memory [19].

Current studies have shown that EGb 761® can efficiently decrease insulin resistance induced by high-fat intake and improve other symptoms of metabolic syndrome [20]. With a model of palmitate-induced insulin resistance, it has been established that EGb 761® decreases insulin resistance through inhibition of stress kinases, NF-[kappa]B, and protein kinase [theta] with partial recovery of insulin signaling [21]. A study on a model of Otsuka Long-Evans Tokushima Fatty rats with obesity and insulin resistance with EGb 761® in the dose of 100 and 200 mg/kg has shown that the extract possesses the dose-dependent effect of decrease of the intima-media ratio, decelerated proliferation of arterial smooth muscle cells. Kaempferol and quercetin possess the highest activity in this regard. Authors conclude that EGb 761® plays a protective role in development of atherosclerosis and can be an atherosclerosis prophylaxis product [10].

In the clinical aspect, the fact that EGb 761® does not influence pharmacokinetics of metformin widely used in treatment of DM-2 is quite important [22].

Depression and anxiety significantly affect quality of life. Experimental studies that have shown ability of EGb 761® to improve symptoms of depression and anxiety [23], including through modulation of secretion of dopamine and serotonin in the brain [24–26], have confirmation in clinical studies [27–29].

5 Conclusions

By matching the available experimental and clinical data, we can conclude that in the setting of DM-2 EGb 761®, by producing a positive effect towards various factors which results from insulin resistance of the brain, improves functions of the brain, which manifests in improvement of main QoL

Table 4 Changes in QoL indicators during treatment with EGb 761®

QOL indicators	Initial data	After 3 months of treatment	After 6 months of treatment
PF	51.07 ± 29.24	65.02 ± 25.12, $p^* = 0.02$	77.12 ± 22.11; $p^* = 0.01$, $p^{**} = 0.02$
RP	39.54 ± 37.24	42.8 ± 42.36, $p^* = 0.05$	52.8 ± 35.36; $p^* = 0.04$, $p^{**} = 0.03$
BP	48.84 ± 25.9	49.84 ± 26.27, $p^* = 0.07$	50.68 ± 25.04; $p^* = 0.06$, $p^{**} = 0.08$
GH	45.86 ± 14.91	55.56 ± 19.35, $p^* = 0.01$	66.78 ± 25.32; $p^* = 0.01$, $p^{**} = 0.03$
VT	48.78 ± 19.64	55.15 ± 21.97, $p^* = 0.03$	68.25 ± 22.88; $p^* = 0.01$, $p^{**} = 0.01$
SF	61.86 ± 24.54	69.67 ± 22.43, $p^* = 0.04$	72.42 ± 35.27; $p^* = 0.04$, $p^{**} = 0.04$
RE	40.48 ± 43.17	47.23 ± 38.96, $p^* = 0.027$	57.87 ± 27.56; $p^* = 0.01$, $p^{**} = 0.02$
MH	55.43 ± 17.76	70.82 ± 19.97, $p^* = 0.01$	82.71 ± 29.82; $p^* = 0.01$, $p^{**} = 0.01$

p^*—significance of differences compared to the initial data (before treatment)

p^{**}—significance of differences when indicators are compared after 3 and 6 months of treatment

indicators in DM-2. EGb 761® in the dose of 240 mg/day can be recommended to all patients suffering from DM-2 for prophylaxis and treatment of cognitive decline and improvement of quality of life. The effect of the product is noted after 3 months of continuous treatment with increase until the sixth month of continuous treatment.

It is necessary to take into account that the level of the QoL in patients with DM is lower in comparison with general population, mainly, in relation to RF ($p < 0.01$) and RE ($p < 0.01$). Cognitive impairments in patients with DM-2 significantly affect the factors of the QoL. Patients with cognitive impairment have statistically lower levels of the QoL ($p < 0.01$). The QoL is adversely affected by both depression and anxiety ($p < 0.01$).

Funding Information The reported study was supported by the program of competitive growth of Kazan Federal University.

References

1. Global report on diabetes. [Internet]. Apps.who.int. 2018 [cited 27 March 2018]. Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf.
2. Quality of Life Assessment: an annotated bibliography [Internet]. Apps.who.int. 1994 [cited 27 March 2018]. Available from: http://apps.who.int/iris/bitstream/10665/61629/1/WHO_MNH_PSF_94.1.pdf.
3. Bosic-Zivanovic, D., Medic-Stojanoska, M., & Kovacev-Zavisic, B. (2012). The quality of life in patients with diabetes mellitus type 2. *Vojnosanitetski Pregled, 69*(10), 858–863.
4. Esin, R., Khairullin, I., Esin, O., & Abakumova, A. (2016). Quality of life in patients with type 2 diabetes mellitus. *BioNanoScience, 6*(4), 502–507.
5. Folstein, M., Folstein, S., & McHugh, P. (1975). Mini-mental state. *Journal of Psychiatric Research, 12*(3), 189–198.
6. MoCA Montreal—cognitive assessment [Internet]. MoCA Montreal—cognitive assessment. [cited 27 March 2018]. Available from: http://www.mocatest.org/wp-content/uploads/2015/tests-instructions/MoCA-Test-Russian_2010.pdf.
7. Atkinson, T., & Ryan, J. (2007). The use of variants of the trail making test in serial assessment. *Journal of Psychoeducational Assessment, 26*(1), 42–53.
8. Zigmond, A., & Snaith, R. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370.
9. Ware, J., Snow, K., Kosinski, M., & Gandek, B. (1997). *SF-36 health survey*. Boston: The Health Institute, New England Medical Center.
10. Lim, S., Yoon, J., Kang, S., Choi, S., Cho, B., Kim, M., et al. (2011). EGb761, a Ginkgo biloba extract, is effective against atherosclerosis in vitro, and in a rat model of type 2 diabetes. *PLoS One, 6*(6), e20301.
11. Silva, G. (2011). Neuroprotective action of Ginkgo biloba on the enteric nervous system of diabetic rats. *World Journal of Gastroenterology, 17*(7), 898.
12. Saini, A., Taliyan, R., & Sharma, P. (2014). Protective effect and mechanism of Ginkgo biloba extract-EGb 761 on STZ-induced diabetic cardiomyopathy in rats. *Pharmacognosy Magazine, 10*(38), 172.
13. Welt, K., Weiss, J., Martin, R., Hermsdorf, T., Drews, S., & Fitzl, G. (2007). Ginkgo biloba extract protects rat kidney from diabetic and hypoxic damage. *Phytomedicine, 14*(2–3), 196–203.
14. Wei, Z., Wei, Z., ShanShan, X., & QiChong, X. (2013). GW24-e2480 Ginkgo biloba attenuates oxidative DNA damage of human umbilical vein endothelial cells induced by intermittent high glucose. *Heart, 99*(Suppl 3), A95.2–A9A96.
15. Liu, X., Hao, W., Qin, Y., Decker, Y., Wang, X., Burkart, M., et al. (2015). Long-term treatment with Ginkgo biloba extract EGb 761 improves symptoms and pathology in a transgenic mouse model of Alzheimer's disease. *Brain, Behavior, and Immunity, 46*, 121–131.
16. Xie, H., Wang, J., Yau, L., Liu, Y., Liu, L., Han, Q., et al. (2014). Catechins and procyanidins of Ginkgo biloba show potent activities towards the inhibition of β-amyloid peptide aggregation and destabilization of preformed fibrils. *Molecules, 19*(4), 5119–5134.
17. Talbot, K., Wang, H., Kazi, H., Han, L., Bakshi, K., Stucky, A., et al. (2012). Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *Journal of Clinical Investigation, 122*(4), 1316–1338.
18. Blazquez, E., Velazquez, E., Hurtado-Carneiro, V., Ruiz-Albusac, J. (2014). Insulin in the brain: its pathophysiological implications for states related with central insulin resistance, type 2 diabetes and Alzheimer's disease. *Frontiers in Endocrinology, 5*.
19. Derakhshan, F., & Toth, C. (2013). Insulin and the brain. *Current Diabetes Reviews, 9*(2), 102–116.
20. Cong, W., Tao, R., Tian, J., Zhao, J., Liu, Q., & Ye, F. (2011). EGb761, an extract of Ginkgo biloba leaves, reduces insulin resistance in a high-fat-fed mouse model. *Acta Pharmaceutica Sinica B, 1*(1), 14–20.
21. EGb 761 prevented palmitate-induced insulin resistance in L6 myotubes via the inhibition of stress kinases, NF-[kappa]B, and PK [theta] | American Diabetes Association [Internet]. Professional.diabetes.org. 2007 [cited 30 March 2018]. Available from: https://professional.diabetes.org/abstract/egb-761-prevented-palmitate-induced-insulin-resistance-l6-myotubes-inhibition-stress.
22. Kudolo, G., Wang, W., Javors, M., & Blodgett, J. (2006). The effect of the ingestion of Ginkgo biloba extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects—a double blind placebo-controlled, crossover study. *Clinical Nutrition, 25*(4), 606–616.
23. Zhang, Y., Zhao, Y., Pan, F., & Zhang, P. (2016). EGb761 attenuates depressive-like behaviours induced by long-term light deprivation in C57BL/6J mice through inhibition of NF-κB-IL-6 signalling pathway. *Central European Journal of Immunology, 4*, 350–357.
24. Rojas, P., Serrano-García, N., Medina-Campos, O., Pedraza-Chaverri, J., Ögren, S., & Rojas, C. (2011). Antidepressant-like effect of a Ginkgo biloba extract (EGb761) in the mouse forced swimming test: role of oxidative stress. *Neurochemistry International, 59*(5), 628–636.
25. Yeh, K., Wu, C., Tai, M., & Tsai, Y. (2011). Ginkgo biloba extract enhances noncontact erection in rats: the role of dopamine in the paraventricular nucleus and the mesolimbic system. *Neuroscience, 189*, 199–206.
26. Kehr, J., Yoshitake, S., Ijiri, S., Koch, E., Nöldner, M., & Yoshitake, T. (2012). Ginkgo biloba leaf extract (EGb 761®) and its specific acylated flavonol constituents increase dopamine and acetylcholine levels in the rat medial prefrontal cortex: possible implications for the cognitive enhancing properties of EGb 761®. *International Psychogeriatrics, 24*(S1), S25–S34.
27. Preuss, U., Bachinskaya, N., Kaschel, R., Wong, J., Hoerr, R., & Gavrilova, S. (2013). 1689—Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized placebo-controlled trial. *European Psychiatry, 28*, 1.
28. Gavrilova, S., Preuss, U., Wong, J., Hoerr, R., Kaschel, R., & Bachinskaya, N. (2014). Efficacy and safety of Ginkgo biloba

extract EGb 761®in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. *International Journal of Geriatric Psychiatry, 29*(10), 1087–1095.

29. Hoerr, R., Nacu, A. (2016). Neuropsychiatric symptoms in dementia and the effects of Ginkgo biloba extract EGb 761® treatment: Additional results from a 24-week randomized, placebo-controlled trial. *Open Access Journal of Clinical Trials, 1*.