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LONG-TERM EFFECTS OF QUERCETIN ON OXIDATIVE STRESS PARAMETERS AND NITRIC OXIDE METABOLISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Introduction. Type 2 diabetes mellitus is associated with oxidative stress, impaired antioxidant defence, and dysregulation of nitric oxide metabolism, all of which contribute to the development of vascular and metabolic complications. The use of bioflavonoids, particularly quercetin, represents a promising approach for correcting these disturbances; however, the duration of persistence of its effects after treatment completion requires further investigation.
Aim. The aim of the study was to evaluate the long-term effects of quercetin on oxidative stress parameters, antioxidant defence, and nitric oxide metabolism in patients with type 2 diabetes mellitus three months after completion of treatment.
Materials and methods. The study involved 29 patients with type 2 diabetes mellitus, with a mean age of 59.41 ± 1.8 years; among them, 17 were men, and 12 were women. The mean duration of diabetes mellitus was 10.07 ± 1.16 years, and the mean body mass index was 30.69 ± 0.9 kg/m². Patients received quercetin in the form of the pharmaceutical preparation «Quertin» at a dose of one tablet twice daily for 20 days. Biochemical parameters were assessed before treatment, immediately after completion of therapy and 3 months after treatment. The activity of inducible NO synthase, constitutive NO synthase isoforms, arginase, superoxide dismutase and catalase, as well as malondialdehyde concentration, were determined.
Results. Following treatment, superoxide dismutase activity increased from 7.185 ± 0.174 to 15.54 ± 0.479 and remained elevated at 13.08 ± 0.381 after 3 months. Catalase activity increased from 1.538 ± 0.062 to 3.024 (2.924-3.137), while after 3 months it was 2.581 ± 0.073. The level of malondialdehyde decreased from 29.12 (26.79-32.87) to 14.03 ± 0.391 and, after 3 months, remained lower than baseline at 15.03 ± 0.549. After 3 months, the activity of constitutive NO synthase isoforms increased to 0.068 (0.055-0.189), whereas arginase activity remained below baseline values. Integral comparison of the parameters at the three time points revealed statistically significant differences ($H = 45.97$; $p < 0.0001$). Differences between the post-treatment values and those obtained after 3 months were not statistically significant ($p = 0.2488$). **Conclusions.** The use of quercetin in patients with type 2 diabetes mellitus was associated with sustained positive changes in antioxidant defence parameters, lipid peroxidation and nitric oxide metabolism 3 months after completion of treatment.

Keywords: **type 2 diabetes mellitus, quercetin, oxidative stress, nitric oxide, arginase, long-term outcomes**

INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains one of the most pressing medical and social challenges in contemporary medicine due to its high prevalence, chronic progressive course, and significant risk of cardiovascular, renal, neurological, and microvascular complications. Despite the availability of effective glucose-lowering therapies, achieving glycaemic control is not always accompanied by complete correction of the metabolic disturbances underlying disease progression and the development of diabetic complications [1].

One of the key pathogenetic mechanisms in T2DM is oxidative stress, which develops as a result of chronic hyperglycaemia, insulin resistance, activation of systemic low-grade inflammation, and excessive production of reactive oxygen species [2,3]. An imbalance between

free radical generation and the activity of antioxidant defence systems leads to damage to lipids, proteins, vascular endothelium, and cellular membranes. One of the laboratory manifestations of this process is an increased level of malondialdehyde (MDA), which reflects the intensity of lipid peroxidation, accompanied by a reduction in the activity of antioxidant enzymes, particularly superoxide dismutase (SOD) and catalase.

Dysregulation of the nitric oxide (NO) system also plays a key role in the development of vascular and metabolic disturbances in diabetes mellitus. Physiologically, NO is involved in the regulation of vascular tone, microcirculation, platelet aggregation, and endothelial function. However, in T2DM, an imbalance occurs between constitutive and inducible NO synthase isoforms, which may be accompanied by excessive NO production via the inducible pathway, development of nitrosative stress, and a reduction in the bioavailability of physiologically active NO [4]. Arginase (ARG) is also important, as it competes with NO synthase for their common substrate, L-arginine. Increased arginase activity may limit the NO synthase-dependent pathway of L-arginine metabolism and contribute to the progression of endothelial dysfunction.

In this context, a promising approach is the use of agents capable of influencing not only individual metabolic parameters but also the pathogenetic mechanisms of oxidative and nitrosative stress. One such compound is quercetin, a bioflavonoid with antioxidant, anti-inflammatory, and potentially endothelium-protective properties. Its biological effects are associated with its ability to reduce free radical formation, modulate redox-sensitive signalling pathways, influence the NF-κB/Nrf2 system, and enhance enzymatic antioxidant responses [5-9].

In a previous study, it was demonstrated that the inclusion of quercetin in the comprehensive therapy of patients with T2DM is associated with a reduction in oxidative stress manifestations, in particular a decrease in MDA levels, an increase in SOD and catalase activity, as well as changes in parameters of the nitric oxide system [10]. A similar pathogenetic direction of these changes was also demonstrated in the assessment of disturbances in the nitric oxide cycle and oxidative stress in patients with prediabetes [11].

At the same time, most studies investigating the effects of quercetin on metabolic and biochemical disturbances in diabetes mellitus primarily assess immediate treatment outcomes. However, in clinical practice, it is critically important not only to demonstrate improvement in parameters immediately after completion of therapy, but also to determine the duration of persistence of this effect. Long-term outcomes make it possible to evaluate the stability of the therapeutic response, the potential impact of the drug on pathogenetic mechanisms of the disease, and the appropriateness of its inclusion in the comprehensive correction of metabolic disturbances in patients with T2DM.

Therefore, it is relevant to investigate the dynamics of oxidative stress parameters, antioxidant defence, and nitric oxide metabolism not only immediately after quercetin administration, but also in the long-term period, namely 3 months after completion of treatment. Such an approach makes it possible to assess the stability of the observed biochemical changes and to determine whether the beneficial effects of quercetin persist after discontinuation of its use.

AIM

To evaluate the long-term effects of quercetin on oxidative stress parameters, antioxidant defence, and nitric oxide metabolism in patients with type 2 diabetes mellitus 3 months after completion of treatment.

MATERIALS AND METHODS

The study involved 29 patients with T2DM, who underwent examination and treatment at the Municipal Enterprise «2 City Clinical Hospital» of Poltava. The mean age of the examined patients was 59.41 ± 1.8 years. According to gender distribution, the study group consisted of 17 men and 12 women. The mean duration of diabetes mellitus was 10.07 ± 1.16 years, and the mean body mass index was 30.69 ± 0.9 kg/m².

The diagnosis of T2DM was established in accordance with the Unified Clinical Protocol of Primary and Specialized Medical Care «Type 2 Diabetes Mellitus in Adults,» approved by Order No. 1300 of the Ministry of Health of Ukraine dated July 24, 2024 [12]. Prior to inclusion in the study, patients were receiving oral glucose-lowering medications; the mean glycated hemoglobin level was 8.66 ± 0.29%. All study participants received recommendations regarding rational nutrition and individualized physical activity.

Prior to inclusion in the study, all patients provided written informed consent. The study was conducted in accordance with the principles of bioethics and regulatory requirements for clinical research involving human participants. The study design and protocol were approved by the Bioethics Committee of Poltava State Medical University, Protocol No. 248 dated April 23, 2026.

Patients were prescribed quercetin in the form of the pharmaceutical preparation «Quertin.» The drug was administered orally 30 minutes before meals at a dose of one tablet twice daily; patients were advised to chew the tablet and drink a small amount of water. The duration of the treatment course was 20 days. The manufacturer of the preparation is Public Joint-Stock Company «Scientific and Production Center «Borshchahivskiy Chemical-Pharmaceutical Plant».

The activity of inducible NO synthase (iNOS), constitutive NO synthase isoforms (cNOS), ARG, SOD and catalase, as well as the concentration of free MDA, were determined in the patients. Blood samples for assessment of these parameters were collected at three time points: before treatment initiation, immediately after completion of therapy and 3 months after treatment. This approach made it possible to evaluate both the immediate and long-term dynamics of the investigated biochemical markers. Methodological approaches to the assessment of oxidative and nitrosative stress parameters were applied in accordance with previously described biochemical methods [13].

Statistical analysis of the obtained results was performed using Microsoft Office Excel 2019 and GraphPad Prism 8.0 software. Data distribution normality was assessed using the D'Agostino-Pearson test. Under conditions of normal distribution, the results were presented as mean values and standard error of the mean (M ± m), whereas in the case of non-normal distribution, the data were presented as median and interquartile range, Me (Q1–Q3). Comparisons of parameters at three time points were performed using the Kruskal-Wallis test and repeated-measures ANOVA. To assess differences in the dynamics of biochemical markers in patients with type 2 diabetes mellitus after quercetin administration across the three time points, a mixed-effects model was applied, in which the biomarkers were considered dependent variables and time was treated as the independent variable. Equality of variances between two samples was assessed using Fisher's F-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The dynamics of the parameters analyzed at three time points: before treatment, after treatment and 3 months after treatment are presented in Table 1.

Table 1

Dynamics of biochemical markers in patients with type 2 diabetes mellitus following quercetin administration

Parameter, units	Before treatment	After treatment	3 months after treatment	p
SOD, arbitrary units	7.185±0.174	15.54±0.479	13.08±0.381	<0.0001
Catalase, μkat/g	1.538±0.062	3.024 (2.924-3.137)	2.581±0.073	<0.0001
MDA, μmol/L	29.12 (26.79-32.87)	14.03±0.391	15.03±0.549	0.0007
cNOS, μmol/min per g protein	0.038 (0.02-0.057)	0.05±0.004	0.068 (0.055-0.189)	<0.0001
iNOS, μmol/min per g protein	0.463 (0.272-0.618)	0.462 (0.272-0.618)	0.53±0.065	<0.0001
ARG, μmol/min per g protein	1.472±0.021	0.668 (0.618-0.755)	0.861 (0.829-0.884)	<0.0001

Comparison of the parameters at three time points revealed statistically significant overall differences in biochemical markers ($H = 45.97$; $p < 0.0001$).

At the same time, one-way ANOVA demonstrated statistically significant differences between baseline and post-treatment values ($p < 0.0001$), as well as between baseline values and those measured 3 months after treatment ($p < 0.0001$). No statistically significant differences were observed between post-treatment values and those obtained 3 months after treatment ($p = 0.2488$).

The findings of the study demonstrated a marked increase in the activity of the enzymatic antioxidant defence system after treatment. SOD activity was 7.185 ± 0.174 before treatment, increased to 15.54 ± 0.479 after completion of the therapeutic course, and remained elevated at 13.08 ± 0.381 three months after treatment (Fig. 1).

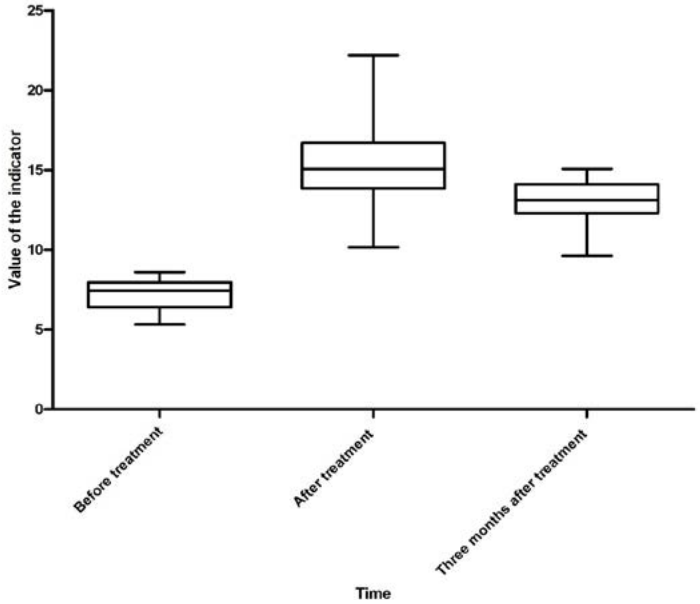

Fig. 1. Dynamics of SOD (arbitrary units) in patients with type 2 diabetes mellitus following quercetin administration

A similar dynamic was observed for catalase activity. Before treatment, catalase activity was 1.538 ± 0.062; it increased to 3.024 (2.924-3.137) after treatment, and amounted to 2.581 ± 0.073 three months after treatment (Fig. 2).

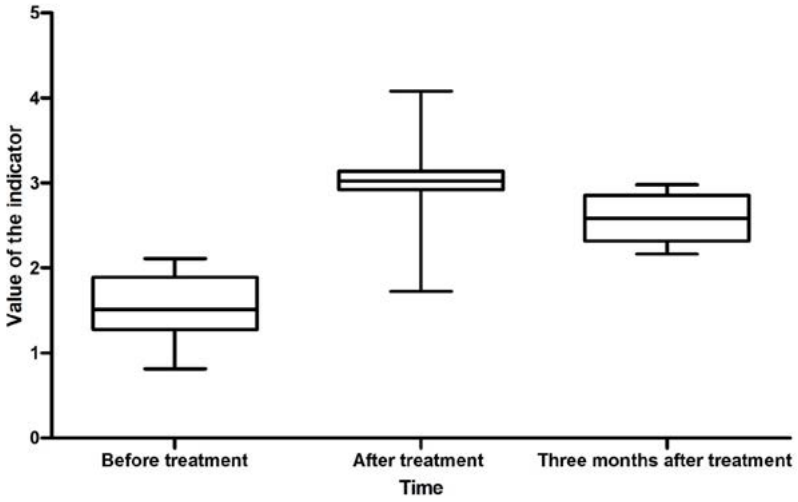

Fig. 2. Dynamics of catalase (μkat/g) in patients with type 2 diabetes mellitus following quercetin administration

The obtained results demonstrate that quercetin administration was associated with activation of two key enzymes of the antioxidant defence system – SOD and catalase. SOD ensures the dismutation of the superoxide anion radical, whereas catalase is involved in the decomposition of hydrogen peroxide.

The level of MDA, a marker of lipid peroxidation intensity, was 29.12 (26.79-32.87) before treatment. After treatment, it decreased to 14.03 ± 0.391, and 3 months after treatment it was 15.03 ± 0.549. Thus, quercetin administration resulted in an almost two-fold reduction in MDA levels. In the long-term period (3 months after treatment), this parameter remained significantly lower than the baseline level. A slight increase in MDA compared with the immediate post-treatment value did not return to baseline levels (Fig. 3).

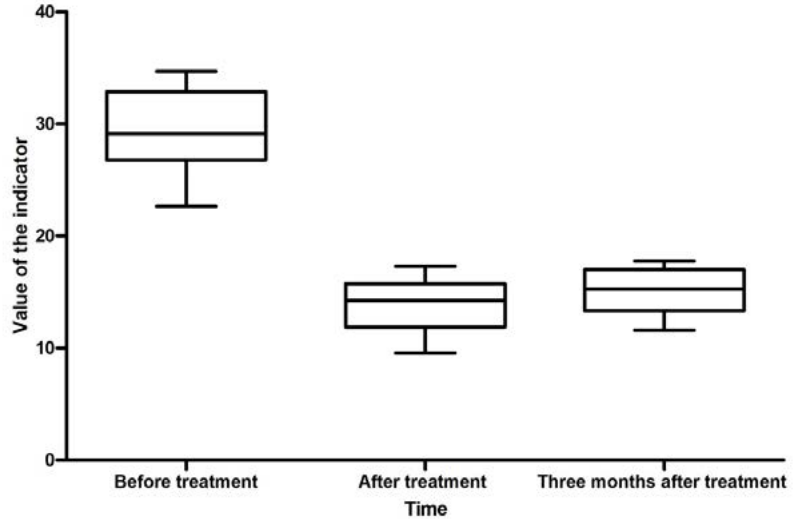

Fig. 3. Dynamics of MDA (μmol/L) in patients with type 2 diabetes mellitus following quercetin administration

The analysis of NO-synthase system parameters showed that cNOS activity was 0.038 (0.02-0.057) before treatment. After treatment, it increased to 0.05 ± 0.004, and 3 months after treatment it reached 0.068 (0.055-0.189) (Fig. 4).

Unlike most other parameters, cNOS demonstrated not only maintenance but also a further increase in the long-term period.

At the same time, iNOS activity did not show a clear decreasing trend. It was 0.463 (0.272-0.618) before treatment, 0.462 (0.272-0.618) after treatment, and 0.53 ± 0.065 three months after treatment (Fig. 5).

The most favourable dynamics in the NO system were primarily associated with an increase in cNOS activity, whereas iNOS remained relatively stable.

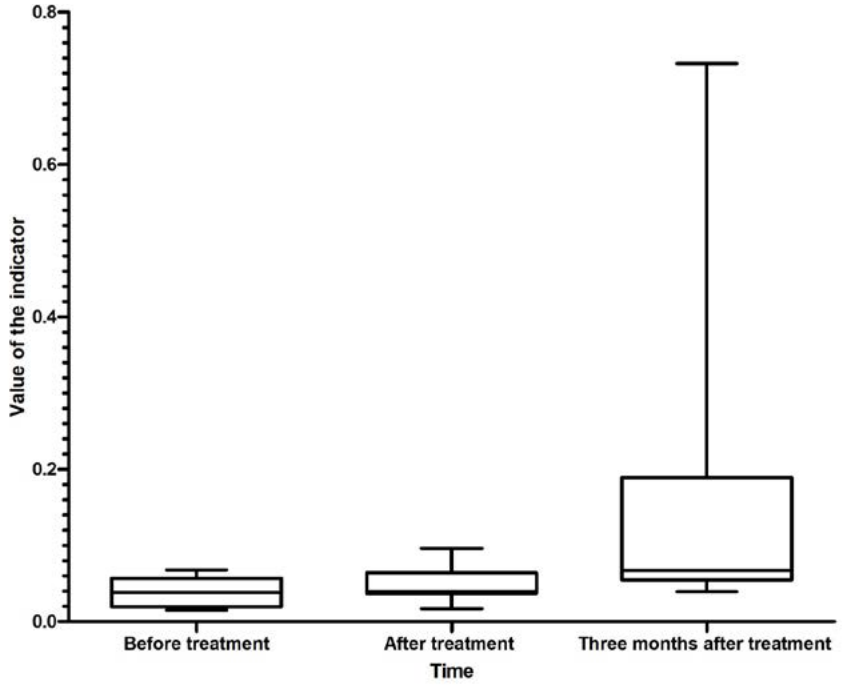

Fig. 4. Dynamics of cNOS (μmol/min per g protein) in patients with type 2 diabetes mellitus following quercetin administration

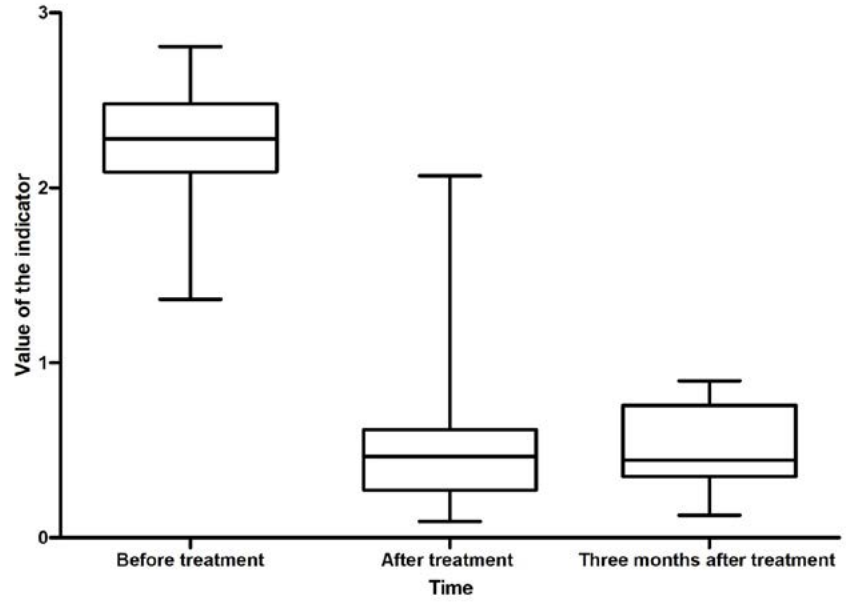

Fig. 5. Dynamics of iNOS (μmol/min per g protein) in patients with type 2 diabetes mellitus following quercetin administration

ARG activity was 1.472 ± 0.021 before treatment. After treatment, it decreased to 0.668 (0.618-0.755), and 3 months after treatment it was 0.861 (0.829-0.884) (Fig. 6).

Thus, after treatment, a marked decrease in arginase activity was observed. Three months later, this parameter slightly increased compared with the immediate post-treatment value; however, it remained lower than the baseline level. This indicates the persistence of a favourable trend in the arginase pathway in the long-term period.

Overall, the integrated comparison of the studied parameters across the three time points demonstrated statistically significant differences ($H = 45.97$; $p < 0.0001$).

The mixed-effects model confirmed a significant effect of treatment on biochemical markers ($p < 0.0001$); however, it did not confirm a statistically significant effect of time on changes in these parameters ($p > 0.05$).

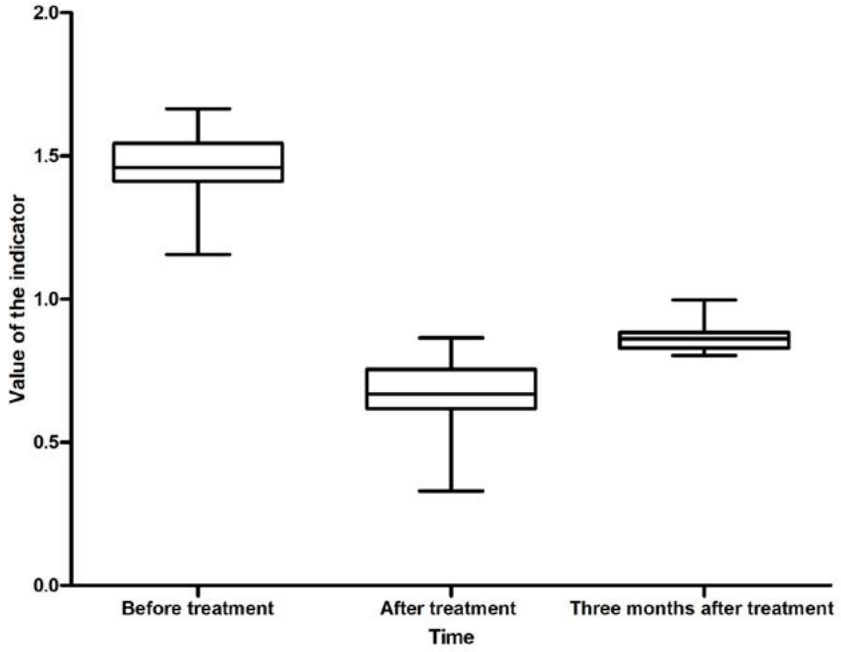

Fig. 6. Dynamics of ARG (μmol/min per g protein) in patients with type 2 diabetes mellitus following quercetin administration

The findings show that the observed post-treatment changes were not transient. Three months after the completion of therapy, the parameters remained statistically different from baseline values; however, no statistically significant differences were found compared with the immediate post-treatment results.

DISCUSSION

The obtained results demonstrate that quercetin administration in patients with T2DM was associated with a comprehensive positive dynamics of the studied biochemical parameters. The most pronounced changes concerned an increase in the activity of antioxidant enzymes, namely SOD and catalase, and a reduction in MDA levels, indicating a decrease in oxidative stress intensity.

Quercetin is a polyphenolic compound capable of modulating redox-sensitive signalling pathways, particularly NF-κB and Nrf2, which may explain its antioxidant and anti-inflammatory properties [5-9, 14]. The maintenance of elevated SOD and catalase activity 3 months after treatment completion may indicate a prolonged effect of quercetin on the enzymatic antioxidant defence system.

Although SOD activity in the long-term period was slightly lower than immediately after treatment, it remained substantially higher than baseline levels. This suggests that activation of antioxidant defence was not limited to a short-term effect but persisted for 3 months after therapy completion. A similar pattern was observed for catalase activity, which remained elevated compared with baseline, suggesting sustained enhancement of peroxide detoxification capacity.

Overall, the coordinated increase in SOD and catalase activity may indicate partial restoration of the enzymatic antioxidant response in patients with T2DM. Importantly, both parameters remained higher than baseline at 3 months, supporting the hypothesis that quercetin may contribute not only to short-term antioxidant correction but also to a more sustained adaptive response.

The obtained data also indicate a reduction in lipid peroxidation intensity after treatment, with persistence of this effect in the long-term period. As MDA reflects oxidative damage to cellular membranes, its sustained decrease may represent one of the key markers of quercetin efficacy in correcting oxidative stress. In the context of T2DM, this is particularly relevant, as chronic hyperglycaemia, insulin resistance, and endothelial dysfunction promote excessive reactive oxygen species production and lipid peroxidation, contributing to vascular complications [1-4].

Regarding the nitric oxide system, the most significant changes were an increase in constitutive NO synthase (cNOS) activity and a decrease in arginase (ARG) activity. This pattern is pathogenetically relevant, as arginase competes with NO synthase for their common substrate, L-arginine; therefore, reduced arginase activity together with increased cNOS activity may reflect a more favourable redistribution of L-arginine toward NO synthesis [15, 19].

Unlike most other parameters, cNOS demonstrated not only sustained improvement but also a further increase in the long-term period, suggesting a gradual restoration of physiological NO-dependent endothelial regulation, including vascular tone and microcirculation control. In T2DM, impaired NO bioavailability is a key mechanism of vascular dysfunction; therefore, the observed increase

in cNOS activity at 3 months may be considered a favourable adaptive change.

In contrast, arginase activity decreased after treatment and, although it slightly increased at 3 months compared with the immediate post-treatment level, it remained below baseline. Together with increased cNOS activity, this suggests a sustained shift in L-arginine metabolism towards NO synthase–dependent pathways.

Comparison across the three time points showed that long-term results remained close to post-treatment values. The absence of statistically significant differences between post-treatment and 3-month values indicates stability of the achieved changes. At the same time, significant differences between baseline and 3-month values confirm a sustained therapeutic effect.

The obtained results are consistent with previous studies demonstrating the beneficial effects of quercetin on oxidative stress, nitric oxide metabolism, and arginase activity [10, 11, 15-18]. However, the 3-month follow-up allows these effects to be interpreted not only as an immediate response but also as a sustained biological effect.

This finding supports further research into the optimal frequency of repeated quercetin courses, including evaluation at 3- or 6-month intervals. However, given the absence of a significant time effect in the current analysis, no definitive conclusions can be drawn regarding the necessity of repeated administration, which requires dedicated prospective long-term studies.

CONCLUSIONS

The use of quercetin in patients with T2DM was associated with the maintenance of favourable changes in oxidative stress parameters, antioxidant defence, and nitric oxide metabolism 3 months after treatment completion. The long-term effect was manifested by increased activity of SOD, catalase, and cNOS, as well as decreased MDA levels and arginase activity compared with baseline values. The absence of statistically significant differences between immediate post-treatment results and those obtained after 3 months indicates the stability of the observed changes in the long-term period. These findings suggest that quercetin may be considered a promising component of comprehensive pathogenetic correction of oxidative stress and NO synthase–arginase imbalance in patients with type 2 diabetes mellitus.

Prospects for further research. A promising direction for further research is the assessment of longer-term dynamics of oxidative stress parameters, antioxidant defense and nitric oxide metabolism in patients with type 2 diabetes mellitus after quercetin administration. It is advisable to conduct studies with an extended follow-up period, particularly at 6 and 12 months after therapy completion, as well as to investigate the effectiveness of repeated quercetin courses for maintaining the achieved antioxidant and metabolic effects.

COMPLIANCE WITH ETHICAL REQUIREMENTS

Prior to inclusion in the study, all patients provided written informed consent. The study was conducted in accordance with the principles of bioethics and regulatory requirements for clinical research involving human participants. The study design and protocol were approved by the Bioethics Committee of Poltava State Medical University, Protocol No. 248 dated April 23, 2026.

Study limitations. The limitations of this study include the relatively small sample size, single-center design. These factors should be considered when interpreting the results and planning further studies.

Primary data and materials. The primary data and materials generated and analyzed during the study are available from the corresponding author upon reasonable request.

Declaration of AI use. Artificial intelligence tools were used only for language editing and stylistic improvement of the manuscript. AI was not used to generate primary data, perform statistical analysis, or formulate the scientific conclusions.

FUNDING AND CONFLICT OF INTEREST

The study was performed within the framework of the research project «Development of methods for correcting pathological changes in the digestive system under conditions of civilization diseases,» State Registration No. 0124U001922.

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Shaienko Z. O.[A, B, D, F]

Morokhovets H. Yu.[C, E, F]

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Резюме

ВІДДАЛЕНІ ЕФЕКТИ КВЕРЦЕТИНУ НА ПОКАЗНИКИ ОКСИДАТИВНОГО СТРЕСУ ТА МЕТАБОЛІЗМ ОКСИДУ АЗОТУ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Златослава О. Шаєнко, Галина Ю. Мороховець

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Вступ. Цукровий діабет 2 типу асоціюється з оксидативним стресом, порушенням антиоксидантного захисту та дисрегуляцією метаболізму оксиду азоту, що сприяє розвитку судинних і метаболічних ускладнень. Застосування біофлавоноїдів, зокрема кверцетину, є перспективним підходом до корекції цих порушень; однак тривалість збереження його ефектів після завершення лікування потребує подальшого вивчення.

Мета. Оцінити віддалені ефекти кверцетину щодо показників оксидативного стресу, антиоксидантного захисту та метаболізму оксиду азоту в пацієнтів із цукровим діабетом 2-го типу через 3 місяці після завершення лікування.

Матеріали та методи. У дослідження було включено 29 пацієнтів із цукровим діабетом 2 типу, середній вік яких становив 59,41 ± 1,8 року; серед них було 17 чоловіків і 12 жінок. Середня тривалість цукрового діабету становила 10,07 ± 1,16 року, середній індекс маси тіла – 30,69 ± 0,9 кг/м^2. Пацієнти отримували кверцетин у формі фармацевтичного препарату «Квертин» у дозі 1 таблетки двічі на добу протягом 20 днів. Біохімічні показники оцінювали до лікування, одразу після завершення терапії та через 3 місяці після лікування. Визначали активність індуцибельної NO-синтази, конститутивних ізоформ NO-синтази, аргінази, супероксиддисмутази й каталази, а також концентрацію малонового діальдегіду.

Результати. Після лікування активність супероксиддисмутази підвищилася з 7,185 ± 0,174 до 15,54 ± 0,479 і залишалася підвищеною через 3 місяці – 13,08 ± 0,381. Активність каталази зросла з 1,538 ± 0,062 до 3,024 (2,924-3,137), а через 3 місяці становила 2,581 ± 0,073. Концентрація малонового діальдегіду знизилася з 29,12 (26,79-32,87) до 14,03 ± 0,391 і через 3 місяці залишалася нижчою за вихідний рівень – 15,03 ± 0,549. Через 3 місяці активність конститутивних ізоформ NO-синтази підвищилася до 0,068 (0,055-0,189), тоді як активність аргінази залишалася нижчою за вихідні значення. Інтегральне порівняння показників у трьох часових точках виявило статистично значущі відмінності ($H = 45,97$; $p < 0,0001$). Відмінності між показниками після лікування та через 3 місяці не були статистично значущими ($p = 0,2488$).

Висновки. Застосування кверцетину пацієнтам із цукровим діабетом 2-го типу асоціювалося зі стійкими позитивними змінами показників антиоксидантного захисту, перекисного окиснення ліпідів і метаболізму оксиду азоту через 3 місяці після завершення лікування.

Ключові слова: **цукровий діабет 2 типу, кверцетин, оксидативний стрес, оксид азоту, аргіназа, віддалені результати.**

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