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Original Article

The effect of quercetin on the development of oxidative stress and nitric oxide production in the blood of patients with Type 2 Diabetes Mellitus

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Abstract

Diabetes mellitus is a non-communicable disease that is recognized as a global epidemic and is a leading cause of disability and mortality. An important area of research in diabetology is the creation and implementation of brand-new drugs that affect the key mechanisms of diabetes development and prevent the occurrence or progression of associated complications. The aim of the study is to evaluate the effect of quercetin on the activity of antioxidant enzymes, lipid peroxidation and nitric oxide synthesis in the blood of patients with type 2 diabetes mellitus. Methods and Material. During the study, 36 patients with an average age of 58.86±1.89 years have been examined. The subjects have been treated at the Municipal Institution "2nd City Clinical Hospital" in Poltava in 2023. All subjects were divided into two groups: the experimental group (n=21), which included patients with diagnosed type 2 diabetes mellitus and the control group (n=15), which included individuals without disorders in carbohydrate metabolism. Quercetin enhances antioxidant defense and effectively reduces excessive nitric oxide production, which is of great importance in treating type 2 diabetes mellitus.

Keywords: quercetin, diabetes mellitus, nitric oxide, lipid peroxidation.

Introduction

Diabetes mellitus (DM) is a chronic, non-infectious metabolic disease associated with the development of oxidative stress due to the continuous impact of elevated blood plasma glucose. Diabetes is prevalent in all countries worldwide and is the leading cause of disability and mortality in patients. Although the recent antidiabetic drugs are effective in reducing blood glucose levels, they do not prevent or halt the progression of the disease [1].

Currently, treatment approaches that take into account all pathogenetic mechanisms of complication development in diabetes mellitus have not been fully developed. Therefore, it is important to search for agents that can affect systemic inflammation at various levels of cellular metabolism, the development of oxidative stress and nitric oxide production [2]. Plant-derived polyphenols may be such substances [3].

Quercetin's antioxidant properties, primarily attributed to its ability to inhibit nuclear factor NF-κB signaling and activate its antagonistic counterpart, nuclear factor-erythroid-derived 2-like 2 (Nrf2), underpin many of its pharmacological effects [3]. As known, NF-κB controls the expression of genes that regulate cellular survival and death, influenced by cytokines. NF-κB is a key factor in the development of insulin resistance. Pro-inflammatory cytokines such as IL-6 and TNF-α, along with protein kinase C and IκB kinase (IKK) complex, induce serine phosphorylation of

insulin receptor substrate-1 (IRS-1), impairing insulin signaling and leading to insulin resistance [4, 5]. Furthermore, impaired tyrosine phosphorylation of IRS-1 and phosphoinositide 3-kinase in type 2 diabetes patients results in profound disruptions in glucose transport, phosphorylation and glycogen synthesis [6].

Recent molecular studies have shown that quercetin suppresses NF-κB activation by inhibiting the 26S proteasome, which in turn prevents the ubiquitin-mediated degradation of the inhibitory protein IκB [7]. As a result, the NF-κB complex is not formed, leading to a decrease in the production of pro-inflammatory cytokines and pro-oxidant proteins. Furthermore, quercetin has been reported to suppress the synthesis of p65, a crucial member of the NF-κB family [8]. In patients with stable coronary artery disease, quercetin treatment has been associated with a reduction in the expression of the IkBα gene [9].

However, a major problem with the medical use of bioflavonoids is their insufficient bioavailability. The incorporation of carbohydrate-containing components into this medication improves the solubility and bioavailability of poorly soluble flavonoids [10]. The oral formulation of quercetin allows for prolonged use of the drug, making it suitable for conditions such as stable atherosclerosis, coronary artery disease and others [3, 11].

However, the effectiveness of oral quercetin in influencing various pathogenetic links in the development of type 2 diabetes remains poorly studied.

The aim of this study is to evaluate the effect of quercetin on the activity of antioxidant enzymes, lipid peroxidation and nitric oxide synthesis in the blood of patients with type 2 diabetes mellitus.

This paper represents a segment of the research work, named "Development of means to correct pathological changes in the organs of the digestive system in the context of civilization diseases". State registration number 0124U001922. Duration 2024–2028.

Material and methods

A total of 36 patients, ranging in age from 40 to 78 years (mean age 58.86±1.89), participated in the study, which took place at CE "2nd City Clinical Hospital" in Poltava between September and December 2023. The participants were divided into two groups: the control group (n=15), consisting of individuals without diabetes mellitus, and the experimental group (n=21), comprising individuals diagnosed with type 2 diabetes mellitus.

The clinical study included men and women with a verified diagnosis of type 2 diabetes mellitus. The diagnosis was made in accordance with the "Unified Clinical Protocol for Primary and Specialized Medical Care for Type 2 Diabetes Mellitus in Adults" (Order of the Ministry of Health of Ukraine No. 1300 dated July 24, 2024) [11].

Before participating in the study, patients underwent treatment with oral hypoglycemic agents, and their glycated hemoglobin level averaged 8.75±0.37%. They were also given recommendations on balanced nutrition and assigned specific physical activity routines. All procedures involving the patients were performed after obtaining their signed informed consent and approval from the Biomedical Ethics Commission of Poltava State Medical University (Protocol No. 229 dated 22.08.2024).

The clinical, instrumental, and laboratory examination involved collecting complaints and medical history, conducting objective examinations, recording anthropometric measurements, calculating body mass index, determining blood pressure levels, and performing electrocardiography. All patients underwent conventional laboratory testing using standard methods, including a complete blood count, blood glucose test, glycated hemoglobin test, urine glucose, biochemical blood tests, urinalysis and microalbuminuria test.

The people assigned to the experimental group were given a treatment plan that included taking quercetin ("Quertin" drugs) orally 30 minutes before meals, at a dose of 1 tablet twice a day, to be chewed and swallowed with a small amount of water, for 20 days. The manufacturer is the public joint-stock company Scientific Production Center "Borshchahivskyi Chemical-Pharmaceutical Plant".

All participants underwent biochemical blood analysis. In the control group, blood tests were conducted once, whereas in the experimental group, tests were carried out twice — once before treatment and once after treatment. The blood samples were analyzed for the activity of inducible (iNOS) and constitutive isoforms of NO synthase (cNOS), arginase activity, superoxide dismutase (SOD) activity, catalase levels, and the concentration of free malondialdehyde (MDA).

The total activity of NO-synthases (gNOS) was evaluated by an increase in nitrite concentration after incubation of 0.2 ml of blood plasma in an incubation solution consisting of 2.5 ml of Tris-buffer solution (pH=7.4), 0.3 ml of 320 mM L-arginine solution and 0.1 ml of 1 mM NADH+H solution [12]. Activity of constitutive isoforms of NO-synthase (cNOS) was evaluated

by an increase in nitrite concentration after incubation of 0.2 ml of blood plasma in incubation solution consisting of 2.5 ml of Tris-buffer solution (pH=7.4), 0.3 ml of 320 mM L-arginine solution, 0.1 ml of 1 mM NADH+H solution and 0.1 ml of 1% aminoguanidine hydrochloride solution [12]. The activity of iNOS was calculated as iNOS=gNOS-cNOS. Arginase activity was estimated by an increase in L-ornithine concentration after incubation of 0.1 ml of blood plasma in an incubation solution consisting of 0.5 ml of Phosphate-buffer solution (pH=7.0) and 0.2 ml of 24 mM L-arginine solution [12].

The activity of SOD was calculated based on the inhibition of adrenaline autooxidation by blood plasma SOD. The method was carried out as follows:

1. Adrenaline autooxidation speed in Carbonate-buffer solution (pH=10.2) was estimated on wavelength 405 nm;
2. Inhibition of adrenaline autooxidation by blood plasma SOD was evaluated by the addition of 0.1 ml of blood plasma and 0.5 ml of epinephrine hydro tartrate (1.82 mg/ml) to 4.4 ml of Carbonate-buffer solution (pH=10.2) and subsequent incubation for 5 minutes at t=26oC [13].

Catalase activity was measured by a decrease in hydrogen peroxide concentration after 10 minutes of incubation of 0.2 ml of blood plasma with 2 ml of 0.03% hydrogen peroxide solution freshly prepared from 60% solution at t=26oC [13]. Concentration of free MDA was measured by the formation of a colored product of the reaction of MDA with 1-methyl-2phenyl-indole [13].

The outcomes of the biochemical analyses were statistically evaluated using the Mann-Whitney U test to determine the significance of the differences between the control and experimental groups prior to treatment. The Wilcoxon test was used to compare the pre-and post-treatment results within the experimental group. A difference between the indicators was considered statistically significant if $p<0.05$.

Results and discussion

The development of type 2 diabetes condition is accompanied by a 4.53-fold increase in iNOS activity in the blood compared to this measure in the control group. Similarly, the activity of blood arginase also increased by 1.83 times compared to the control group. At the same time, the activity of cNOS does not change significantly (Table 1). Thus, in type 2 diabetes mellitus, a disruption of normal autoregulation of the nitric oxide cycle is established, as evidenced by The concurrent rise in the activity of arginase and iNOS.

In individuals with type 2 diabetes mellitus, the serum SOD activity before treatment is reduced by a factor of 1.73, and the catalase activity decreases by a factor of 1.87 when compared to the control group. Additionally, the MDA concentration in the blood of these patients increases by 3.53 times prior to treatment relative to the control group (Table 1). These findings suggest that oxidative stress occurs in the blood of individuals with type 2 diabetes mellitus, as reflected by

Table 1: Changes in the biochemical parameters of the blood in both groups (M±m).

Biomarkers	Groups		
	Control, n=15	Experimental, n=21	
		Before the therapy, n=21	After the therapy, n=21
Inducible constitutive isoforms of NO synthase, µmol/min per g of protein	0.51+0.11	2.31+0.05*	0.38+0.04**
Constitutive isoforms of NO synthase, µmol/min per g of protein	0.033+0.005	0.043+0.004	0.052+0.004
Arginase, µmol/min per g of protein	0.82+0.02	1.50+0.02*	0.67+0.03**
Superoxide dismutase, CU	12.11+0.38	7.00+0.21*	15.59+0.47**
Catalase, µkat/g	2.80+0.05	1.50+0.06*	3.00+0.04**
Malondialdehyde, µmol/L	8.47+0.36	29.94+0.71*	14.88+0.35**

Note: * – the difference is notably significant when compared to the control group ($p<0.05$); ** – the difference is statistically meaningful compared to the experimental group prior to treatment ($p<0.05$).

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the higher MDA levels and lower antioxidant enzyme activity.

In people suffering from type 2 diabetes, Quertin administration leads to a 6.08-fold reduction in iNOS activity and a 2.24-fold decrease in arginase activity in the blood compared to the experimental group before treatment. However, Quertin has no statistically significant impact on cNOS activity (Table 1).

In patients with type 2 diabetes mellitus treated with Quertin, SOD activity in the blood increases by 2.23 times, while catalase activity shows a 2.0-fold rise compared to the experimental group before treatment. Additionally, the MDA level in the blood decreases by 2.01 times relative to the pre-treatment level (Table 1).

Many researchers report that activation of the transcription factor NF-κB plays a key role in developing type 2 diabetes mellitus [14–16]. The increased activity of iNOS in the blood of patients with type 2 diabetes mellitus can be explained by the activation of the NF-κB transcription factor, as this enzyme is under direct transcriptional control of NF-κB [17]. The nitric oxide cycle, which includes all isoforms of NO synthases, arginase and the L-arginine-independent mechanism of nitric oxide formation, is a complex self-regulating system. An increase in nitric oxide and L-citrulline production from iNOS under intact physiological self-regulation of the cycle leads to a reduction in arginase activity due to the ability of L-citrulline to inhibit the activity of these enzymes [18]. In our study, the simultaneous increase in iNOS and arginase activity indicates a disruption in the physiological autoregulation of the nitric oxide cycle in the subjects with type 2 diabetes mellitus. Studies on the relationship between arginase activity and the development of type 2 diabetes mellitus have shown that increased arginase 1 activity has a direct correlational relationship with the development of type 2 diabetes mellitus and obesity [19].

Most antioxidant enzymes are under the direct transcriptional control of the NRF family of factors. One of the most active regulators of antioxidant enzyme activity within the NRF factor family is NRF-2. As mentioned earlier, in type 2 diabetes mellitus (T2DM), it is typical to observe the activation of the NF-κB transcription factor, which competes with NRF-2 for CBP coactivators within the cell nucleus, leading to a decreased binding of NRF-2 to its nuclear site [20]. The reduced binding of NRF-2 to its nuclear site, which results in decreased expression of SOD and catalase genes, can explain the reduced activity of these enzymes observed in our study. Additionally, scientific publications provide evidence of the positive effects of NRF-2 activators in reducing oxidative stress in T2DM [21]. Another important pathogenic factor contributing to the increased intensity of lipid peroxidation observed in our study is the increased production of reactive oxygen and nitrogen species in T2DM [22]. One mechanism that may enhance the production of reactive oxygen species is the increased activity of arginases, which promotes the development of endothelial dysfunction and the uncoupling of constitutive NO synthase isoforms from their substrate [23].

The main active component of Quertin is quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one). Quercetin belongs to the polyphenolic compounds and thus has a potent direct antioxidant effect due to the ability of its phenolic groups to absorb electrons and neutralize free radicals [24]. In addition to its direct antioxidant effect, quercetin also has an indirect effect on the activity of antioxidant enzymes through the stimulation of the NRF-2 transcription factor [25]. Quercetin is also a powerful inhibitor of NF-κB transcription factor activation [26]. Therefore, quercetin has a multifaceted effect on the generation and utilization of reactive oxygen species, which could account for the decrease in lipid peroxidation intensity in the blood of individuals suffering from type 2 diabetes who incorporated quercetin into their combination therapy.

The decrease in iNOS activity seen with Quertin administration in patients with type 2 diabetes mellitus can be attributed to quercetin, the key active component in Quertin, which has the ability to reduce the activation intensity of the NF-κB transcription factor [26]. Additionally, scientific literature provides evidence of quercetin's ability to inhibit arginase activity, which may explain the reduction in this enzyme's activity in the blood of type 2 diabetes mellitus patients who were treated with Quertin [27].

Conclusions

The course of type 2 diabetes mellitus leads to the development of oxidative stress in the blood, which is accompanied by hyperproduction of nitric oxide from the inducible isoform of NO synthase. The use of quercetin in patients with diabetes mellitus prevents the development of oxidative damage to the blood by enhancing antioxidant defense. Quercetin restores the impaired physiological regulation of the nitric oxide cycle that occurs in diabetes mellitus. Quercetin is a potent agent in reducing the excessive production of nitric oxide from the inducible form of NO synthase and

in preventing oxidative stress in the blood of individuals with type 2 diabetes mellitus.

Conflict of interest

The authors declare no conflict of interest.

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