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Quercetin effect on endogenous factors of cardiovascular risk and ageing biomarkers in elderly people

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Abstract. The reason for this study was the lack of literature data on the quercetin effect on endogenous cardiovascular risk factors and ageing biomarkers in elderly patients with metabolic syndrome (MS). The results of this study showed that quercetin has a favourable corrective effect on endogenous cardiovascular risk factors in elderly patients with MS, quercetin course increases the resistance of the elderly to the effects of hypoxia, long-term quercetin use (within 3 months) leads to lengthening of telomeres and a decrease in metabolic age, which indicates the presence of a geroprotective effect. The obtained results of the quercetin course application influence on the telomere length show the expediency of continuing the study of this drug as an effective geroprotective agent.

Keywords: quercetin; metabolic syndrome; endogenous factors; ageing biomarkers; geroprotective effect

Changes in various organs and systems that occur during ageing contribute to the development of age-related diseases. Among them, MS is widespread. MS is a combination of endogenous cardiovascular risk factors, type 2 diabetes mellitus, malignant neoplasms, and cognitive impairment [1-3]. The development of MS is based on insulin resistance, which is also one of the main endogenous factors of accelerated human ageing [4].

The main manifestations of MS include disorders of carbohydrate metabolism (prediabetes, type 2 diabetes mellitus), lipid metabolism (increased levels of triglycerides, decreased high-density lipoprotein cholesterol), increased blood pressure, and hemorheological disorders [5]. The frequency of these manifestations increases with age. The development of endothelial dysfunction is characteristic of ageing and MS. Its manifestations are a decrease in endothelium-dependent vasodilation, an increase in the sensitivity of the vascular wall to the action of vasoconstrictor factors, a deterioration in the vasomotor, antiplatelet, antiadhesive, and antithrombotic functions of the endothelium [6,7]. It is also known that with ageing, the body's sensitivity to hypoxia increases and resistance to hypoxia decreases, the level of free oxygen in tissues decreases, the content of under oxidized products increases, and glycolysis reactions are activated [8].

An important molecular marker of ageing is the shortening of the length of telomeres, the end sections of chromosomes [9]. Telomeres shorten with each cell division. Damage to telomeres can lead to the

transition of the cell into a "senile" (corresponding terms are "senile" or "senescent") state. Telomere-induced senescence of postmitotic cells is supposed to be one of the key factors of ageing [10].

Shortening of telomeres leads to a decrease in the proliferative potential and is a marker of cellular ageing. Although the length of telomeres decreases with age in all cell lines, the rate of shortening differs significantly in different tissues of the body and depends on their proliferative activity. Telomere length also decreases in ageing-associated diseases of the cardiovascular system, obesity, type 2 diabetes mellitus, MS, and neurodegenerative diseases [11].

To correct age-related changes in the body, geroprotective agents are used. These include the bioflavonoid quercetin, which has antioxidant, anti-inflammatory, angioprotective, and vasodilating effects [12–14]. In recent years, quercetin has been regarded as a "senolytic" that selectively kills senescent cells [15-17]. The results of previous studies substantiate the use of quercetin for the correction of metabolic disorders [18]. At the same time, there are no published data on the quercetin effect on endogenous cardiovascular risk factors and ageing biomarkers in elderly patients with MS, which was the basis for the study.

Materials and methods.

By the laws of Ukraine and the principles of the Helsinki Declaration on Human Rights, 110 patients with MS in the age group of 60-74 years were examined. MS was diagnosed in the presence of three or more criteria according to ATP III, 2001. There were two groups of patients. Patients of the main group (55 people) took quercetin at a daily dose of 240 mg for 3 months (Quertin, produced by PJSC Borshchagovsky CPP). Patients in the control group (55 people) took a placebo for 3 months. The subjects of both groups took ACE inhibitors, statins, and acetylsalicylic acid (75-100 mg/day) at a constant dose for at least one month before inclusion in the study and during participation in the study as basic therapy.

To assess the state of carbohydrate metabolism, the levels of glucose and insulin in the blood plasma on an empty stomach and during the standard oral glucose tolerance test (SGTT) were determined. Glucose concentration was determined by the glucose oxidase method on a BTS-330 semi-automatic biochemical analyzer, insulin levels were determined on a Multiscan EX analyzer (Labsistems, Finland) by enzyme immunoassay using ELISA kits (DRG, Germany).

The HOMA-IR index (Homeostasis Model Assessment for Insulin Resistance) was used to determine insulin resistance. It was calculated by the formula:

HOMA-IR = (fasting plasma glucose, mmol/l x fasting plasma insulin, μMO/ml) / 22.5.

Serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TG) were also determined using standard biochemical methods on an Autolab autoanalyzer from Boehringer Mannheim.

Skin blood flow volume velocity (SBFV) was determined using a BLF-21D two-channel laser Doppler flowmeter (Transonic Systems Inc, USA). Blood flow studies were performed in the region of the middle third of the inner surface of the forearm. First, the volumetric rate of skin blood flow in the initial state was determined. Then a functional test with reactive hyperemia was performed, to create which, for 3 minutes, the shoulder vessels were clamped with a cuff in which the pressure exceeded the SBP level of the subject by 50 mm Hg. Art. After the restoration of blood flow (cessation of clamping), the blood supply to the tissues increases as a result of vasodilation, which is caused by the release of nitric oxide from the endothelium. During this period, indicators of the maximum volumetric velocity of skin blood flow (SBFV max) and the duration of the period of recovery of SBFV to the initial level (t recovery) were determined. The higher both indicators, the better the functional state of the endothelium of microvessels [19]. To assess the quercetin effect on the body's resistance to hypoxia, a 20-minute hypoxic test was used (breathing with a certified gas mixture with 12% oxygen). It was carried out 2-3 hours after breakfast. Before the hypoxic test (HT), during it, and in the first 5 min after the cessation of HT, blood saturation (SpO2), heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressure (BP) were determined.

Quercetin's effect on the length of telomeric regions was determined by measurement.

The relative length of telomeric regions of chromosomes of peripheral blood leukocytes was determined using a multiplex quantitative real-time polymerase chain reaction (RT-qPCR) [20].

To assess quercetin effect on the rate of metabolic aging, we used the mathematical model of metabolic age that we developed [21]:

Y = 1,90 X1 + 1,30 X2 + 6,68 X3 - 0,18 X4 + 0,10 X5 + 28,74,

where

Y – calculated age, years;

X1 – blood plasma glucose after 2 hours of SGTT, mmol/l;

X2 – cholesterol, mmol/l;

X3 – Very LDL, mmol/l;

X4 – Alanineaminotransferase (AlT), units/l;

X5 – creatinine, μmol/l.

Statistical data analysis was carried out using the STATISTICA 7.0 (StatSoftInc.) software package. During preprocessing, a normal distribution of data was found, which made it possible to use parametric methods. The calculation of the arithmetic means error and the mean error was carried out, to assess the dispersion of the influence of factors, an ANOVA analysis of variance was performed. The statistical significance of the results was assessed by Student's t-test.

Results and discussion.

There was no significant quercetin effect on the variance of fasting glucose concentration (ANOVA, F = 1.5; p = 0.2070). At the same time, a statistically significant e quercetin effect on the dispersion of plasma glucose concentration after 2 hours of SGTT was revealed (ANOVA, F = 7.3; p = 0.0002).

After the course use of quercetin, the frequency of detection of prediabetic disorders of carbohydrate metabolism decreased - increased fasting glycemia (from 51 to 33%) and impaired glucose tolerance (from 44 to 13%). The decrease in plasma glucose levels was accompanied by a trend towards a decrease in the insulin resistance index HOMA-IR (Tab.1).

Table 1.

Glucose concentration and insulin in the blood plasma before and after quercetin course application (M ± m)

Indicators	Control group (n = 55)		Main group (n = 55)	
	Before treatment	After treatment	Before treatment	After treatment
Glucose concentration in the blood plasma on an empty stomach, mmol/l Shift	5.73 ± 009	5.80 ± 0.06 0.07 ± 0.06	6.01 ± 0.11	5.87 ± 0.08 -0.13 ± 0.12
Plasma glucose concentration after 2 hours of SGTT, mmol/l Shift	6.60 ± 0.21	6.7 ± 0.19 0.16 ± 0.13	7.29 ± 0.29	6.51 ± 0.23 -0.76 ± 0.24*#
Plasma insulin concentration, mmol/l Shift	14.01±1.4	13.41 ± 1.26 -0.83 ± 1.2	16.61 ± 1.12	14.6 ± 2.34 -1.48 ± 1.1
Insulin resistance index HOMA Shift	3.86 ± 0.49	3.48 ± 0.37 -0.38 ± 0.31	4.41 ± 0.6	3.77 ± 0.59 -0.56 ± 0.33

Notes: the veracity of change in the indicator under the influence of treatment: * – $p< 0.05$; the veracity of the difference between the indicator shifts in the main and control groups: # – $p< 0.05$.

Under the influence of quercetin course use, there was a statistically significant decrease in the level of total cholesterol and LDL cholesterol in the blood serum. In patients of the control group who did not receive quercetin, the indicators of carbohydrate and lipid metabolism did not change (Tab. 1, 2).

Table 2.

Lipids concentration in the blood serum before and after quercetin course application (M ± m)

Indicators	Control group (n = 55)		Main group (n = 55)	
	Before treatment	After treatment	Before treatment	After treatment
TC, mmol/l Shift	5.77 ± 0.14	5.58 ± 0.15 -0.19 ± 0.14	5.97 ± 0.14	5.53 ± 0.15 -0.40 ± 0.14*
TG, mmol/l Shift	1.27 ± 0.06	1.22 ± 0.07 -0.05 ± 0.06	1.34 ± 0.07	1.24 ± 0.07 -0.10 ± 0.05
HDL, mmol/l Shift	1.59 ± 0.03	1.56 ± 0.03 -0.02 ± 0.03	1.55 ± 0.03	1.59 ± 0.03 0.04 ± 0.03
LDL, mmol/l Shift	3.63 ± 0.13	3.44 ± 0.16 -0.19 ± 0.16	3.82 ± 0.16	3.41 ± 0.14 -0.38 ± 0.14*
Very LDL, mmol/l Shift	0.52 ± 0.02	0.50 ± 0.03 -0.02 ± 0.03	0.60 ± 0.03	0.55 ± 0.03 -0.04 ± 0.02
Atherogenic index Shift	2.68 ± 0.10	2.65 ± 0.12 -0.03 ± 0.13	2.88 ± 0.12	2.51 ± 0.10 -0.35 ± 0.11*

Notes: the veracity of change in the indicator under the influence of treatment: * – $p < 0.05$.

The use of quercetin led to a statistically significant increase in the maximum volumetric velocity of skin blood flow in the test with post-occlusive hyperemia (Tab. 3). The period of recovery of the volumetric velocity of SBFV. Changes in both indicators indicate an improvement in the functional state of the endothelium of microvessels.

An improvement in the functional state of the endothelium under the influence of quercetin was observed in most of the examined patients and was accompanied by an additional statistically significant decrease in systolic blood pressure by 7.2 ± 1.2 mm Hg. Art. ($p < 0.05$) and a trend towards a decrease in diastolic blood pressure by 3.24 ± 1.8 mm Hg. Art. ($p > 0.05$).

Table 3.

SBFV indicators in the test with reactive hyperemia before and after quercetin course application (M ± m)

Indicators	Control group (n = 55)		Main group (n = 55)	
	Before treatment	After treatment	Before treatment	After treatment
SBFV at rest, ml / (min x 100g tissue) Shift	1.08 ± 0.03	1.04 ± 0.02 -0.04 ± 0.03	1.03 ± 0.02	1.05 ± 0.02 0.02 ± 0.03
SBFV max at the peak of reactive hyperemia, ml / (min x 100g tissue) Shift	5.65 ± 0.23	5.25 ± 0.27 -0.41 ± 0.27	5.69 ± 0.25	6.67 ± 0.24 0.97 ± 0.26*#
Recovery time of SBFV to the initial level, s Shift	110.78 ± 5.35	101.36 ± 4.20 -9.42 ± 6.02	102.18 ± 5.15	123.04 ± 4.78 20.85 ± 4.62*#
Endothelial function, % Shift	74.57 ± 4.66	66.0 ± 4.51 -8.57 ± 5.23	77.88 ± 4.89	93.68 ± 5.11 15.80 ± 5.34*#

Notes: the veracity of change in the indicator under the influence of treatment: * – $p < 0.05$; the veracity of the difference between the indicator shifts in the main and control groups: # – $p < 0.05$.

Thus, with long-term quercetin course use, the manifestations of MS, which are also biomarkers of ageing, decrease.

To assess quercetin's effect on the body's resistance to hypoxia, a dosed hypoxic test was performed before and after the course of the drug. with the determination of blood saturation index (SpO_2). It was found that quercetin course use led to a less significant decrease in SpO_2 under hypoxic conditions. At the same time, no significant changes in SpO_2 dynamics were observed in the control group after 3 months of observation. Moreover, the decrease in blood saturation during dosed hypoxia in the subjects of this group was more significant (Tab. 4).

Table 4.

Blood saturation and indicators of the cardiovascular system in the HP before and after quercetin course application (M ± m)

Indicators	Control group (n = 55)		Main group (n = 55)	
	Before treatment	After treatment	Before treatment	After treatment
SpO_2, %				
before HP	97.3 ± 0.6	97.2 ± 0.3	97.0 ± 0.6	97.3 ± 0.5
for 20 min HP	84.0 ± 2.6	82.6 ± 2.5	84.4 ± 1.9	89.9 ± 1.4
the shift for 20 min HP	-13.3 ± 2.3*	-14.6 ± 2.4*	-12.6 ± 1.7*	-7.4 ± 1.2*#
HR, min^{-1}				
before HP	69.8 ± 3.4	66.2 ± 2.6	68.5 ± 3.3	69.0 ± 2.1
for 20 min HP	74.4 ± 3.1	75.4 ± 2.9	73.8 ± 2.5	74.2 ± 2.4
the shift for 20 min HP	4.7 ± 1.5*	5.3 ± 1.6*	5.3 ± 1.8*	5.1 ± 1.8*
Systolic BP, mm Hg. Art.				
before HP	131.0 ± 3.3	135.6 ± 5.1	133.9 ± 4.0	125.3 ± 3.7
for 20 min HP	140.9 ± 3.2	146.8 ± 6.8	144.2 ± 4.3	131.9 ± 3.9
the shift for 20 min HP	9.9 ± 2.3*	10.3 ± 4.4*	10.3 ± 2.4*	5.8 ± 2.3*#
Diastolic BP, mm Hg. Art.				
before HP	79.0 ± 2.3	83.8 ± 4.3	84.4 ± 2.2	75.6 ± 3.5
for 20 min HP	87.74 ± 4.3	89.8 ± 4.7	92.3 ± 3.0	81.7 ± 3.2
the shift for 20 min HP	7.7 ± 2.4*	7.3 ± 4.9	7.8 ± 2.6*	6.1 ± 2.2*

Notes: shifts of all indicators during hypoxia: * – $p< 0.05$; the veracity of blood saturation during hypoxia under the influence of quercetin: # – $p<0.05$.

It should be noted that under the influence of quercetin course application for 20 min of HP, there was a decrease in both systolic and diastolic BP, as well as a decrease in the increase in systolic BP (Tab. 4). These changes indicate a decrease in the stress response of the cardiovascular system and an increase in the overall resistance of the body to the effects of hypoxia. The lack of literature data on quercetin's effect on telomere length was the basis for the study of changes in this ageing biomarker in the control and main groups of patients.

The impact of quercetin course use or placebo was assessed using the Wilcoxon test (Figure). In the group of patients taking quercetin, there was a statistically significant increase in the length of leukocyte telomeres from 0.71 (0.63 - 0.82) to 0.78 (0.68 - 0.85) ($p = 0.02$). In the control group, telomere length did not change during the 3-month observation period (before - 0.77 (0.67 - 0.98), after - 0.77 (0.67 - 0.84), $p = 0.35$).

Given the small sample size (30 people in the main and control groups) and significant dispersion of telomere length, the result can be considered clinically significant.

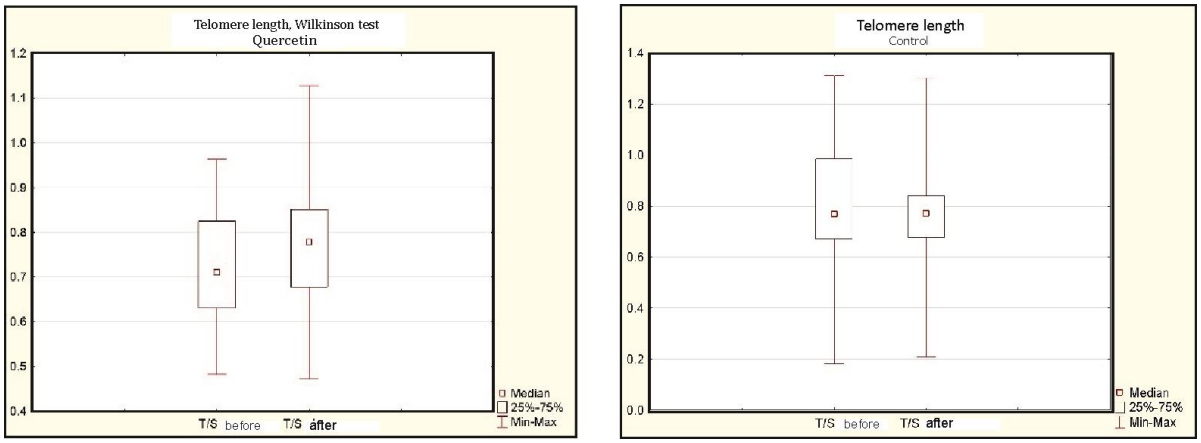

Figure. Telomere length in the control and main groups before and after the quercetin course application

Quercetin is known to be a senolytic that eliminates senescent cells [22]. Senescent cells produce a range of signalling molecules, such as interleukin-6 and interleukin-8, leading to chronic inflammation. The removal of senescent cells leads to a reduction in inflammation and oxidative stress, which in turn can lead to telomere lengthening. Studies have shown that the metabolic age indicator, calculated using the multiple regression equation, decreased by 2.26 ± 0.61 years under the influence of quercetin use.

Table 5

Changes in metabolic age by quercetin course

Statistical indicators	Quercetin	Placebo
An average offset (M)	-2.26	-0.70
The error of the mean (m)	0.61	0.64
Student's criterion (t)	3.70*	1.09

Notes: the veracity of change by quercetin: * – $p < 0.01$

The decrease in metabolic age by quercetin indicates the presence of its geroprotective effect in patients with MS. Our results confirm the data of the literature, especially those where attention was paid to the fact that the use of quercetin positively affects carbohydrates [18, 23] and lipid metabolism [24], leading to a decrease in elevated blood pressure [26]. O. Yu. Biryukov (2011) showed that quercetin use in male rats with MS reduces the manifestations of impaired carbohydrate tolerance and increases the insulin sensitivity coefficient [18]. Improvement of insulin sensitivity in rats with insulin resistance with quercetin use was shown in the experimental work of P. Srinivasan et al. [23]. S. Jeong et al. obtained a decrease in TC and TG under quercetin influence in rats with alloxan diabetes [24]. The favourable quercetin effect on the state of carbohydrate metabolism in elderly patients with MS that we have established can be explained by its protective effect on β-cells of the pancreatic islets and an increase in insulin secretion [25], as well as an improvement in insulin sensitivity [24]. Vasoprotective effects of quercetin are carried out by reducing the inflammatory process activity in the vascular endothelium, increasing the activity of endothelial NO-synthase (eNOS), which leads to an increase in the level of nitric oxide in endothelial cells. This improves endothelial function [26].

Thus, a favourable corrective quercetin effect on such endogenous risk factors for developing cardiovascular diseases as pre-diabetic disorders of carbohydrate metabolism, dyslipidemia, endothelial dysfunction, arterial hypertension, and low resistance to hypoxia have been established. This may determine quercetin's therapeutic efficacy in elderly patients with manifestations of MS. The results of the course use of

quercetin on telomere length were particularly interesting and promising, which encourages further study of this drug as an effective geroprotective agent.

Conclusions:

1. Quercetin has a favourable corrective effect on endogenous cardiovascular risk factors in elderly patients with MS. This is evidenced by the improvement in carbohydrate and lipid metabolism, vasomotor function of the endothelium of microvessels, and lowering blood pressure after a course of quercetin.
2. The quercetin course increases the resistance of the elderly to the effects of hypoxia.
3. Long-term quercetin use (for 3 months) in elderly patients with MS leads to lengthening of telomeres and a decrease in metabolic age, which indicates the presence of a geroprotective effect.

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Conflicts of Interest: The authors declare no conflict of interest.

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