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INFLUENCE OF PHARMACOLOGICAL CORRECTION OF MAGNESIUM DEFICIENCY ON PSYCHOLOGICAL STATUS AND FUNCTIONAL-BIOCHEMICAL INDICATORS IN YOUNG MEN

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The purpose of the study was to evaluate the effect of magnesium deficiency correction with magnesium orotate therapy on anxiety levels, diastolic function parameters, and physical performance in young men. Seventy-six young men (mean age 28.5±5.5 years) without cardiovascular pathology and any somatic diseases in their medical history were examined, among whom 51.3 % were diagnosed with hypomagnesemia, of whom 20 (group 1) were prescribed magnesium orotate (32.8 mg of magnesium) (Magnorot, "Wörwag Pharma", Germany) at a dose of 500 mg three times a day. Group 2 consisted of 19 individuals who were not prescribed magnesium supplements. The study lasted 8 weeks. It was found that a significant proportion of the young men examined had a significant decrease in serum magnesium concentration, along with increased anxiety, signs of diastolic dysfunction, and decreased physical performance. It was shown that 8 weeks of magnesium orthoate therapy helped achieve target serum magnesium levels, along with improved diastolic function, a positive effect on physical performance, and a reduction in reactive and personal anxiety levels to normal values. It was determined that the addition of magnesium orotate to young men for 8 weeks was safe; no adverse events were reported.

Key words: serum magnesium content, hypomagnesemia, anxiety, diastolic function, physical performance, young men, magnesium orotate.

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ВПЛИВ ФАРМАКОЛОГІЧНОЇ КОРЕКЦІЇ ДЕФІЦИТУ МАГНІЮ НА ПСИХОЛОГІЧНИЙ СТАТУС ТА ФУНКЦІОНАЛЬНО-БІОХІМІЧНІ ПОКАЗНИКИ У ЧОЛОВІКІВ МОЛОДОГО ВІКУ

Метою дослідження було оцінити вплив корекції дефіциту магнію за допомогою терапії оротатом магнію на рівень тривоги, параметри діастолічної функції і фізичної працездатності у чоловіків молодого віку. Обстежено 76 молодих чоловіків (середній вік 28,5±5,5 роки) без серцево-судинної патології та будь-яких соматичних захворювань в анамнезі, серед яких у 51,3 % визначено гіпомагніємію, із них 20 (1 група) призначався оротат магнію (32,8 мг магнію) (Магнерот, «Вьорваг Фарма», Німеччина) по 500 мг тричі на добу. У 2-у групу увійшли 19 осіб, яким препарати магнію не призначались. Тривалість дослідження була 8 тижнів. Встановлено, що у значної частини обстежених молодих чоловіків виявлено достовірне зниження концентрації магнію в сироватці крові, поряд з підвищенням рівня тривоги, наявністю ознак діастолічної дисфункції та зниженням фізичної працездатності. Показано, що 8-тижнева терапія ортоатом магнію сприяла досягненню цільових рівнів магнію в сироватці крові, поряд з покращенням показників діастолічної функції, позитивним впливом на фізичну працездатність, а також знизити рівні реактивної та особистої тривожності до їх нормальних значень. Визначено, що додавання оротату магнію молодим чоловікам протягом 8 тижнів було безпечним; небажаних явищ не зареєстровано.

Ключові слова: вміст магнію в сироватці крові, гіпомагніємія, тривога, діастолічна функція, фізична працездатність, чоловіки молодого віку, оротат магнію.

The work is a fragment of the research project "To determine the features of immunocytokine imbalance in comorbid patients with hypertension and type 2 diabetes and cardiovascular and renal complications", state registration No. 0123U101711.

Cardiovascular disease is the leading cause of death worldwide [7]. Metal ions have been shown to be important regulators of cardiovascular function, and disturbances in metal metabolism may be associated with an increased risk of cardiovascular disease [8]. Numerous epidemiological studies, randomized controlled trials, and meta-analyses have demonstrated an inverse relationship between magnesium intake or serum magnesium levels and cardiovascular disease. This suggests that low magnesium levels are associated with hypertension, coronary artery calcification, ischemic heart disease, stroke, atrial fibrillation, heart failure, and cardiac mortality [10].

Research data evidence that a large number of people are regularly deficient in magnesium [3]. In addition, the need for magnesium may increase under the influence of factors such as psychological stress, high calcium intake and high fiber/phytate intake, etc. [2]. Magnesium deficiency is exacerbated by factors

associated with its insufficient absorption, increased excretion or increased consumption, physical overload, alcohol abuse, medications, etc. [4].

Magnesium orotate is a magnesium-containing drug that not only participates in magnesium metabolism, but also has an independent metabolic effect. Orotic acid stimulates ATP synthesis. Due to the fact that 90 % of intracellular magnesium is associated with ATP, the relative increase in intracellular ATP deposition by orotic acid improves magnesium fixation in cells. The cardioprotective effect of orotic acid is mediated through the regulation of the enzyme N-acetylglucosaminetransferase, inhibition of intracellular phosphodiesterase and modulation of the coenzyme PQQ with anti-inflammatory, antioxidant and neuroprotective effects.

The purpose of the study was to assess the effect of correcting magnesium deficiency using magnesium orotate therapy on the level of anxiety, parameters of diastolic function, and physical performance in young men.

Materials and methods. In the first stage of the study, 76 young men (mean age 28.5±5.5 years) without cardiovascular pathology and any somatic diseases in history were examined to identify the prevalence of hypomagnesemia among young men and to determine the dependence of magnesium content on the level of anxiety. Informed consent was a condition for participation in the study.

Exclusion criteria were: cardiovascular diseases (myocarditis, hypertension, heart defects, ischemic heart disease, cardiomyopathies), somatic diseases, excess body weight, dyselectrolyte disorders.

All patients underwent a general clinical examination, which included a questionnaire to identify risk factors for cardiovascular diseases, anthropometric measurements, a medical physical examination, including office blood pressure measurement, a complete blood count and urine analysis, a biochemical blood test with determination of fasting glucose, lipid metabolism indicators, creatinine (with calculation of GFR according to the CKD-EPI formula), and a 12-lead ECG. The concentration of magnesium in the blood serum (normal range – 0.85–1.2 mmol/l) was determined on an automatic biochemical analyzer "Humalyzer 2000" (Germany).

In 39 (51.3 %) of the examined young men, hypomagnesemia was determined based on the concentration of magnesium in the blood serum. Normal magnesium content in the blood serum was determined in 37 (48.7 %) of the examined individuals who were included in the control group.

The main stage of the study, aimed at assessing the effectiveness of pharmacological correction of magnesium deficiency with magnesium orotate, included 39 examined men (mean age 28.3±5.2 years) with hypomagnesemia, who were divided into 2 groups by random sampling. The 1st group included 20 patients who were prescribed magnesium orotate (32.8 mg of magnesium) in the form of the pharmacological drug Magnerot (Wörwag Pharma, Germany) 500 mg three times a day. The 2nd group included 19 people who were not prescribed magnesium drugs. The duration of the study was 8 weeks.

Before the study began, all subjects received information about the importance of a balanced diet, including foods rich in magnesium.

All examined individuals underwent a dosed physical activity test (cycle ergometry, according to the protocol of R. Bruce, 1971) with the achievement of submaximal (85 %) heart rate (HR) by age and sex. The working capacity and tolerance of physical activity were assessed by calculating the maximum oxygen consumption (MOC) at the last stage of the load in metabolic units (MET).

The assessment of structural and functional parameters of the heart was performed on a GE Medical Systems (Germany) device with a Doppler sensor that allows operation in M- and B-modes and has a power Doppler sensor that makes it possible to determine the function of the left ventricle (LV) diastole in the pulse-wave mode. To characterize the systolic function of the heart, the ejection fraction (EF) of the LV was determined according to Simpson. According to echocardiography, the systolic function of the LV was preserved in all subjects.

The transmitral blood flow was analyzed according to the main measurements: E (maximum flow velocity of the early filling period), A (maximum flow velocity of the late filling period), E/A ratio. The kinetics of the fibrous ring of the mitral valve were also determined: early velocity e′ of diastolic movement of the lateral (e`lateral) and septal (e`septal) parts with calculation of the average value of the velocity of early diastolic movement of the fibrous ring (e`mean); left atrial volume (LAV) and LAV index (iLAV). The ratio of the transmitral flow velocity to the average velocity of the fibrous ring of the mitral valve E/e`, which indirectly reflects the LV filling pressure, was calculated.

To assess situational and personal anxiety, the C. Spielberg Anxiety Questionnaire was used, which contains 40 questions. The result was evaluated as follows: up to 30 points – low anxiety, 31–45 – moderate anxiety, 46 and more – high anxiety.

Statistical processing of the research results was carried out using the STATISTICA 10.0 program and a package of application programs. The arithmetic means of the studied values, standard deviations, and representativeness errors were calculated. To identify the relationship between the studied values, Spearman correlation analysis was used. The difference in indicators in the groups was assessed using the Mann-Whitney test and the Student test. The significance level p was taken to be less than 0.05.

Results of the study and their discussion. In the initial conditions, the examined men of groups 1 and 2 were comparable in age, office blood pressure, presence of magnesium metabolism disorders, psychoemotional state parameters, LV diastolic function indicators and physical performance.

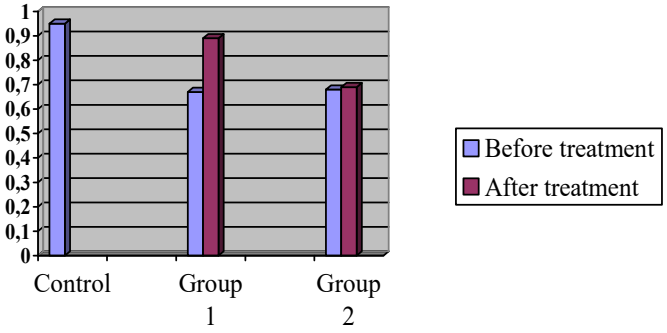

Fig. 1. Dynamics of magnesium content in blood serum in young people examined.

The dynamics of serum magnesium concentration after 8 weeks of observation is presented in Fig. 1.

After 8 weeks of observation, correction of magnesium deficiency to target values was determined in all patients of group 1. At the same time, no significant changes in serum magnesium content were observed in individuals of group 2. Thus, the lack of pharmacological correction of hypomagnesemia did not allow achieving target values of serum magnesium content only by alimentary means.

Analysis of the psychoemotional state at baseline showed that 84.6 % of the examined men with hypomagnesemia had an increase in anxiety levels according to the C. Spielberg scale (Table 1).

Table 1

Main psychological characteristics of the examined individuals at 8-week follow-up (M±m)

Parameters	Group 1 (n=20)		Group 2 (n=19)		Control group (n=37)
	Before treatment	After treatment	Before treatment	After treatment	
Reactive anxiety, scores	46.5±3.9	28.7±3.7	46.7±4.1	46.3±3.7	28.1±1.5
Personal anxiety, scores	47.3±3.8	28.8±3.5	47.8±4.3	47.1±3.6	28.5±1.7

Note: * – significant compared to baseline (p<0.001).

After 8 weeks of taking magnesium orotate, 95 % of young men in group 1, according to the C. Spielberg scale, reached a normal level of anxiety. Against the background of magnesium orotate therapy, there was a decrease in the levels of reactive and personal anxiety by 38.3 % and 39.1 % (p<0.001), respectively, which contributed to an increase in the functional capabilities of the body against the background of an improvement in the psycho-emotional state. At the same time, in people in group 2, no significant changes in the reduction of the levels of reactive and personal anxiety were identified.

When analyzing the parameters of LV diastolic function, it was found that in the examined men of group 1 after treatment with magnesium orotate, there was a significant decrease in the E/A ratio by 11.8 % and the integral index of diastolic function E/e` by 11.0 % (all p<0.05), which indicated an improvement in diastolic function. At the same time, no changes in the parameters of diastolic function were detected in group 2 after 8 weeks of observation (Figs. 2, 3).

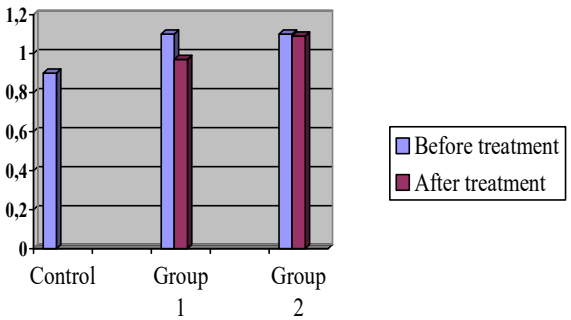

Fig. 2. Changes in the E/A ratio after 8 weeks of observation in young subjects.

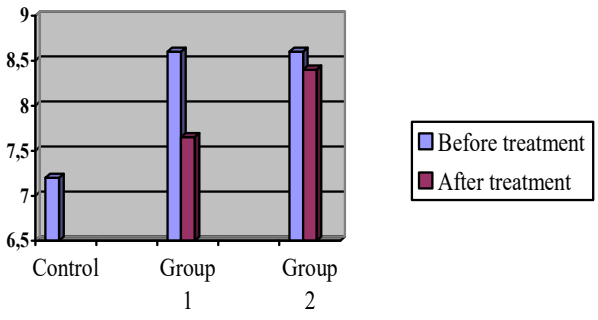

Fig. 3. Changes in the ratio of transmitral flow velocity to the average velocity of the fibrous ring of the mitral valve E/e` after 8 weeks of observation in young subjects.

When assessing physical performance according to the test with dosed physical activity in the initial conditions, it was found that 87.2 % of the examined men with hypomagnesemia had reduced values

of this indicator (7.8±0.9 MET) compared to the control group (10.2±0.6 MET). After 8 weeks, the physical performance indicator in group 1 increased by 17.8 % ($p<0.05$) and did not change significantly in people in group 2 (Fig. 4).

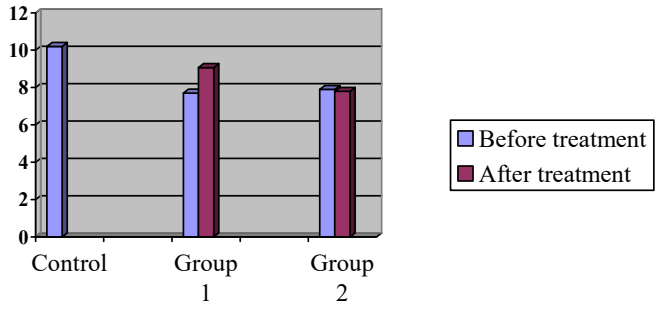

Fig. 4. Dynamics of physical performance according to the test with dosed physical activity during 8 weeks of observation in the examined young people.

It should also be noted that no adverse events were observed in individuals in group 1 during the entire observation period. No adverse events were reported during the course of treatment.

Hypomagnesemia is a very common condition, especially in people with comorbidities, but it is under-recognized compared to other electrolyte abnormalities. Magnesium deficiency, which is widespread in the population, and stress in general may increase the risk of health consequences.

Epidemiological data indicate that total magnesium intake (food, beverages, supplements) was below the recommended daily intake for 45.2 % of all adults. Thus, among adults over 19 years of age, 52.0 % of men and 50.7 % of women had magnesium intakes below the daily intake [3]. In our sample of young men, decreased serum magnesium concentrations were found in 51.3 % of those surveyed.

Magnesium is a micronutrient and intracellular cation responsible for various biochemical reactions related to energy production and storage, control of neuronal and vasomotor activity, cardiac excitability, and muscle contraction. Magnesium acts as a cofactor in over 600 biochemical reactions. Magnesium has been shown to be vital for the regulation of cardiovascular function and maintenance of blood pressure by controlling cell membrane potential; it helps activate Na+, K+- ATPase and counteracts some of the effects of calcium [5]. Magnesium has been shown to have anti-inflammatory and antioxidant properties that may improve lipid metabolism and reduce the risk of atherosclerosis [10]. Magnesium plays a key role in nervous system function, and its deficiency can lead to various neurological symptoms and complications, including neuromuscular hyperexcitability, muscle twitching and spasms, tremors, and convulsions [11]. Magnesium deficiency can lead to impaired physical performance [13].

A definite association between magnesium levels and cardiovascular disease demonstrates that low magnesium levels are generally correlated with increased disease risk [9]. Magnesium deficiency has been shown to contribute to vascular stiffness, oxidative stress, and arrhythmias, thereby increasing the risk of cardiovascular disease [14].

Although free magnesium is physiologically active, total serum magnesium is the most commonly measured and used for clinical purposes. However, such tests are used inappropriately, resulting in a large number of patients with hypomagnesemia remaining underdiagnosed and untreated.

In our research, 8 weeks of magnesium orotate supplementation helped correct serum magnesium levels in 100 % of the men examined.

Previous research has shown that magnesium ions function as NMDA receptor antagonists in the body. Some studies have also shown that magnesium may exhibit some level of agonist activity at GABA-A receptors [12]. Most clinical studies have demonstrated positive results on sleep quality and anxiety in various populations [12].

The therapeutic options for anxiety disorders are gradually expanding, and in recent years both pharmacological and non-pharmacological treatments have become available. Clinical studies investigating the interaction of magnesium with key mediators of the physiological stress response have shown that magnesium plays a key inhibitory role in the regulation and neurotransmission of the normal stress response. It is believed that stress can increase the loss of magnesium, causing a deficiency, which in turn can increase the body's susceptibility to stress, leading to a vicious cycle.

On the other hand, magnesium deficiency may contribute to the development of cardiovascular diseases. The mechanisms of such changes include inflammatory stress, oxidative stress, lipid metabolism disorders, endothelial dysfunction, and dysregulation of cellular ion channels, transporters, and signaling, etc. Magnesium plays a key role in modulating neuronal excitation, intracardiac conduction, and myocardial contraction. Although the exact mechanisms of magnesium effects on cardiac function are not well understood, experimental studies have shown that magnesium supplementation improves cardiac function by eliminating mitochondrial dysfunction and reducing oxidative stress in cardiomyocytes.

It was experimentally established that in animals with chronic diabetes, in which cardiac dysfunction was not accompanied by histological signs of hypertrophy or fibrosis of cardiac cells, magnesium improved diastolic function and mitochondrial activity [1].

Our data on the positive effect of 8-week magnesium orthoatom therapy in young men with increased anxiety testified functional, rather than structural, changes in the pathogenesis of left ventricular diastolic dysfunction.

Magnesium deficiency is observed in many physiological and pathological conditions (imbalanced nutrition, diabetes, cardiovascular diseases, etc.). Magnesium ions are important in the implementation of immune reactions, inflammation, nervous and muscular excitability [14]. Magnesium plays an important role in glucose metabolism through various mechanisms: glucose homeostasis; regulation of phosphorylation; magnesium also has a fundamental role for the activity of many key enzymes. In addition, during physical exertion, hypomagnesemia leads to depletion of glucose levels, which causes a further decrease in performance with an increase in lactate accumulation and increased muscle pain. This is a manifestation of ultrastructural muscle damage that occurs after physical exertion [6]. It has been proven that magnesium deficiency reduces performance and enhances the negative effects of strenuous physical exercise. Therefore, magnesium supplements or higher dietary magnesium intake may be beneficial for physically active individuals with low or deficient magnesium levels [13].

Despite the widely recognized role of magnesium in maintaining human health, the optimal approach to assessing magnesium status is a matter of debate. The results of our research showed that 8 weeks of magnesium oroate supplementation had a positive effect on physical performance in young men with hypomagnesemia.

Conclusions

1. Insufficient serum magnesium, which contributes to the development of cardiovascular disease, is a common condition and requires careful attention for preventive purposes.

2. A significant proportion of the young men examined showed a significant decrease in serum magnesium concentration, which was accompanied by an increase in anxiety levels, signs of diastolic dysfunction, and decreased physical performance.

3. An 8-week magnesium oroate therapy contributed to achieving target serum magnesium levels, along with improved diastolic function, positive effects on physical performance, and a reduction in reactive and personal anxiety levels to their normal values.

4. Magnesium orotate supplementation in young men for 8 weeks was safe; no adverse events were reported.

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