Magnesium deficiency is observed in many physiological and pathological conditions (imbalanced diet, diabetes, cardiovascular diseases, etc.). Magnesium ions are of great importance in the realization of immune reactions, inflammation, nervous and muscular excitability. The deficiency of magnesium is one of the main causes of stress and low stress resistance. Reduction of magnesium content destabilizes the systems responsible for adaptation and facilitates its sensitization, what determines anxiety and high stress level of patients. Understanding the mechanisms of magnesium involvement in the pathogenesis of stress and the development of a stress reaction will allow a family physician to assess the clinical manifestations of magnesium deficiency early in order to provide proper therapy for its correction.

Key words: magnesium, magnesium deficiency, stress, pathogenesis of stress, stress resistance.

Magnesium is a physiological regulator of cellular excitability and is absolutely necessary for normal functioning of the processes of nerve and muscle cell depolarization [8]. It is a cofactor of more than 300 enzymes, many of which are necessary for normal functioning of the nervous system, thus indicating a potentially important role of magnesium in maintaining physiological processes and in the pathological states of the central nervous system [2]. The magnesium content in the body is 17 mmol/kg. The daily recommended amount of magnesium for males is 350 mg, for females – 280 mg. At a young age, for the persons engaged in manual labor, athletes, pregnant and lactating women the requirement of magnesium may increase (additionally for 150 mg/day) [9].

It is believed that magnesium deficiency is a result of both insufficient consumption and excessive excretion or disturbance of homeostasis [4]. Lifestyle factors (specifically changes in the diet, intake of caffeine, alcohol, drugs) and insufficient intake of minerals with food (such as fresh vegetables and fruits) have led to an increase in the number of research studies evaluating the potential relation between magnesium deficiency and numerous health indicators [28]. Chronic magnesium deficiency is often observed in patients with diabetes mellitus, arterial hypertension, atherosclerosis, epilepsy, osteoporosis, etc. A deficiency of magnesium occurs during intake of some drugs [proton pump inhibitors, thiazide diuretics (hydrochlorothiazide), loop diuretics (furosemide) especially with prolonged use, aminoglycosides (gentamycin, tobramycin, amikacin), etc.].

It was demonstrated that acute stress is associated with an increase of the magnesium content in blood plasma and its increased excretion with urine [21]. The transfer of magnesium from the intracellular space to the extracellular one is initially of protective nature and is targeted at the reduction of the unfavorable consequences of stress. However, prolonged stress leads to progressive deficiency of magnesium with the corresponding negative consequences for the organism [29]. In addition, stress and hypomagnesemia potentiate negative effects of each other, creating a vicious circle. The decrease in the ratio of Mg\(^{2+}\)/Ca\(^{2+}\) in response to stress increases the secretion of catecholamines [17]. Magnesium deficiency also promotes the secretion of vasoconstrictors and platelet coagulation factors, increases the ratio of thromboxane B\(_2\) and prostaglandin I\(_2\) (TxB\(_2\)/PGI\(_2\)) and enhances intravascular coagulation [26]. It should be emphasized that deficiency of magnesium in itself does not cause a certain pathology, but reduces tolerance to secondary stress [26].

Magnesium affects a number of mediator systems. It inhibits the secretion of excitatory neurotransmitters and also acts as an antagonist of glutamate N-methyl-D-aspartate (NMDA) receptors [33]. Magnesium is also a physiological antagonist of calcium ions, competing with it in contrast to the blockers of fast and slow calcium
channels not only in the structure of the cell membrane, but also at all levels of the intracellular system. Thus, magnesium prevents excessive penetration of calcium ions inside the cell by blocking ion channels of NMDA receptors, thereby inhibiting the development of excitotoxicity. Magnesium ions are GABA receptor agonists (gamma-aminobutyric acid type A) [32], they increase the reuptake of glutamate by stimulation of Na+/K+-ATP-ase and are associated with mitochondrial ATP-dependent potassium channel activity [14].

It is observed that psychological stress promotes oxidative stress, mainly auto-oxidation of catecholamines. It is shown, that psychological stress enhances lipid per-oxidation, increases the formation of markers of oxidative DNA damage and reduces antioxidant activity of plasma [31]. All this corresponds to a decrease in the concentration of magnesium in the blood.

The stressors (physiological or psychological) activate the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Thus, the secretion from the hypothalamus of corticotropin-releasing factor is observed, which stimulates the anterior portion of the pituitary gland, where adrenocorticotropic hormone (ACTH) starts to be synthesized intensively. The latter stimulates the release of glucocorticoids (cortisol) from the adrenal cortex [22]. Corticotropin-releasing factor (CRF) is a neurotransmitter involved in the coordination of endocrine, vegetative, behavioral and immune reactions to stress, and the administration of it causes stress-like conditions [20].

In addition, magnesium has a direct or indirect effect on the activity of a number of neurotransmitters and neurohormones mentioned. Thus, it was shown that addition of magnesium chloride (MgCl₂) to the incubation medium neutralizes the glutamate-induced secretion of CRF. It is observed that magnesium stabilizes the receptor binding of corticoliberin. At the same time magnesium stimulates Na+/K+-ATP-ase, what leads to a decrease of the sensitivity of CRF receptors [15]. In addition, under the influence of magnesium the secretion of ACTH and adrenocortical sensitivity decrease [11]. It has been experimentally established that the administration of angiotensin II by microinjection into the lateral ventricles of the brain increases the secretion of ACTH and arginine-vasopressin via corticoliberin stimulation. It is proposed that magnesium stimulates the suppression of the activity of the hypothalamic-pituitary-adrenal axis opposite to the effects of angiotensin II [24].

It was observed that in mice with a genetically low level of magnesium in blood, noradrenaline levels were significantly higher in comparison to the mice with high magnesium level and outbred animals [12]. Under the influence of the noise stress more restless behavior was observed in mice with genetically low magnesium level and significantly higher levels of noradrenaline in the brain (+17%) and urine (+200%) compared to the animals with genetically high magnesium content [25]. It has been demonstrated that magnesium has a direct suppressive effect on the activity of the locus coeruleus region and that magnesium deficiency increases sensitivity to stress.

It is proved that under the influence of stress the exchange of serotonin in the brain – in the hypothalamus, locus coeruleus, closely associated with the limbic system – is intensified. Magnesium participates as a cofactor in the synthesis of serotonin, increasing the activity of serotonin receptors thus directly stimulating the neurotransmission mediated by 5-HT1A receptors [10].

Magnesium deficiency is characterized by multiple symptoms and syndromes, the earliest of which are the deviations in functioning of the nervous and cardiovascular systems, the formation of connective tissue dysplasia. The main clinical manifestations of hypomagnesemia include: an increase in neuromuscular excitability (tremor, fasciculation [involuntary contractions of particular muscle fiber bundles], tetany and positive Chvostek and Trousseau symptoms, although some of these signs may be determined by the concomitant hypocalcemia), headaches, hyperemotionality, generalized anxiety, panic attacks, insomnia, fatigue and asthenia. In presence of these symptoms the content of magnesium in blood plasma and erythrocytes, calcium in blood plasma and daily magnesiuria, calciuria should be assessed and magnesium load test should be performed [3].
During the experiment [18] in rats with magnesium deficiency, an insignificant increase in the level of corticosterone in blood plasma, increased irritability and aggressive behavior, as well as higher mortality rate were observed in comparison with the control group. It is generally believed that, in response to psychological stress, individuals with type A behavior experience an increased release of catecholamines and cortisol, and therefore a decrease in magnesium levels and an increase of the risk of cardiovascular events compared to the behavior of type B [20].

Magnesium increases the activity of the enzyme serotonin-N-acetyltransferase involved in the biosynthesis of melatonin, which regulates the circadian rhythm of sleep-wakefulness. Therefore, when magnesium is insufficient, melatonin deficiency may induce sleep disturbances, particularly reduction of night sleep or insomnia [7]. It has been experimentally established that deficiency of magnesium causes sleep disturbances [16]. Thus, the deficiency of magnesium in the ration for 4 weeks led to a decrease of the melatonin content in blood plasma from 4 to 7 hours of night time compared to the animals provided with magnesium (50 vs. ± 5 vs., 75 pg/ml ± 7 pg/ml) [16]. Clinical studies showed that intake of magnesium medications led to sleep normalization in patients with chronic fatigue and stress disorders [1].

It was demonstrated that in presence of headache there is a decrease in the amount of magnesium in the brain and/or peripheral nerves, what leads to an increase in the ratio of Ca\(^{2+}\)/Mg\(^{2+}\) and subsequent hyperexcitability of cells and tissues [2]. In case of magnesium deficiency the excitation of the receptors to glutamate enhances the flow of calcium ions into neurons and potentiates the development of excitotoxicity [19]. Cellular deficiency of magnesium also leads to the activation of the Ca\(^{2+}\)-dependent inflammatory cascade with uncontrolled release of substance P and nitric oxide (II), causes spasm of cerebral vessels, increases platelet aggregation, thereby enhances vasoactive action of serotonin and reduces the effect of prostacyclin-mediated relaxation of smooth vascular musculature [23]. Due to this fact, magnesium deficiency is assumed to be involved in the pathogenesis of primary types of headache (migraine, tension headache, cluster headache) with the realization through the mechanisms of central and peripheral sensitization [2]. It was found that magnesium deficiency occurs in more than half of the patients with headache. Thus, the concentration of magnesium in monocytes, erythrocytes and platelets is reduced by 40–50% in patients with headaches [1].

Common clinical symptoms of magnesium deficiency and physiological manifestations of acute reaction to stress should be taken into account. Thus, leading clinical manifestations of stress – tachycardia, increased blood pressure, headaches, emotional lability, decreased mental alertness, spasms and convulsions – coincide with the symptoms of magnesium deficiency [3, 6].

In modern conditions a person is constantly in close contact with the stress factors of various nature. Scientific and technological progress, deterioration of the environment, the growth of emotional tension in society led to a significant increase of various pathologies, in the etiopathogenesis of which the main role belongs to stress. The complexity, dynamism and contradictory nature of life require from a person to find the best alternatives to difficulties and conflicts, as well as all sorts of crises – from personal to economic ones.

In order to overcome difficult life situations, a person uses behavioral reactions, ranging from lifestyle improvement to self-destructive behavior (for example, smoking, alcoholism, drug addiction, overeating, etc.) or risky activities. It is proved that resistance to stresses differs significantly in the population. The genetically determined level of excitability of the nervous system is a risk factor for the development of post-stress pathological conditions and determines the specificity of their manifestation, provided by various cytogenetic and molecular-cellular mechanisms [5].

Moreover, in persons with autodestructive (self-destructive) behavior hypomagnesemia is more likely to be observed, since alcohol increases the excretion of magnesium from the body [13]. Thus, in case of chronic alcoholism hypomagnesemia develops due to an increase of the magnesium excretion by the kidneys, its insufficient intake with food by the reason of poor nutrition and limited absorption as a result of
proliferative and inflammatory processes in the intestine. Magnesium is a natural glutamate antagonist in NMDA receptors in the brain. Consequently, individuals with chronic alcohol dependence suffer more often due to the significant activity of NMDA during the abstinence periods, what leads to an increased activation reaction of the autonomic nervous system (excitation). In the experiment in rat astrocyte culture, a decrease in magnesium, stimulated by alcohol, led to the violation of calcium level control in the cytoplasm and bioenergetic processes in the mitochondria, leading to overload with calcium ions, ischemia and stroke [34].

Eating disorders are also usually associated with hypomagnesemia, which may be accompanied by hypokalemia, hypocalcemia and hypophosphatemia [4]. Moreover, the content of magnesium in the food of the Western world population is constantly decreasing. People with malnutrition, often accompanied by chronic stressful situations, need magnesium supplements because increased consumption of carbohydrates, fats, coffee and carbonated beverages reduce magnesium level in the organism [3].

Beneficial effects of additional magnesium administration are conditioned by a decrease in the activity of glutamatergic synapses of central neurons, especially those participating in the reward system activated by stress, and modulating effect on the binding of opioid receptors [30]. In addition, administration of magnesium indirectly affects neurogenesis in the hippocampus via influencing corticosteroid hormones, and thus may correct behavior in drug-addicted persons [27].

**Conclusion.** Magnesium is one of the vitally important biologically active microelements, the fourth most common cation in the body and is found mainly in bone, muscle and nerve tissues. It affects the processes of neuromuscular transmission, microcirculation, blood coagulation, energy and electrolyte metabolism, cell growth, etc., what accounts for normal function of nearly all body systems. Magnesium deficiency is one of the main causes of stress and low stress tolerance. Reduction of magnesium content destabilizes the systems responsible for adaptation and facilitates its sensitization, what determines anxiety and high stress susceptibility of patients. It should be emphasized, that normal magnesium content is necessary to be maintained during the periods of intense stress load. Understanding the mechanisms of magnesium participation in the pathogenesis of stress and the development of a stress response will allow a family physician to assess the clinical manifestations of magnesium deficiency early in order to provide proper therapy for its correction.

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ДЕФИЦИТ МАГНИЯ И СТРЕСС
И. И. Князькова, М. В. Богун, В. А. Головачёва, И. В. Лещина (Харьков)

Дефицит магния отмечается при многих физиологических и патологических состояниях (небалансированное питание, сахарный диабет, сердечно-сосудистые заболевания и др.). Ионы магния имеют важное значение в реализации иммунных реакций, воспалении, нервной и мышечной возбудимости. Дефицит магния является одной из основных причин стресса и низкой стрессоустойчивости. Снижение содержания магния дестабилизирует системы, ответственные за адаптацию, и способствует её сенситизации, что определяет тревожность и высокую стрессоспособность пациентов. Понимание механизмов участия магния в патогенезе стресса и развитии стресс-реакции позволит врачу общей практики своевременно оценить клинические проявления дефицита магния с целью проведения мероприятий по его коррекции.

Ключевые слова: магний, дефицит магния, стресс, патогенез стресса, стрессоустойчивость.


О. В. КУРАТА, Г. В. ЧЕРКАСОВА

ЛЕПТИН ТА ІНСУЛІНОРЕЗИСТЕНТНІСТЬ У ХВОРИХ НА ОСТЕОАРТРИТ У ПОЄДНАННІ З ОЖИРІННЯМ І ДИНАМІКА ЇХ РІВНІВ НА ФОНО ЛІКУВАННЯ СИМПТОМАТИЧНИМИ ПРЕПАРАТАМИ ШВИДКОЇ ДІЇ (напроксен натрію)
ДЗ «Дніпропетровська медична академія МОЗ України» <gt1@dsma.dp.ua>

Мета дослідження – визначити рівень лептину та інсулінорезистентності у хворих на остеоартрит (OA) залежно від ожиріння та вплив лікування із застосуванням напроксена натрію. Дослідження проводилися на базі відділення ревматології КЗ «Дніпропетровська обласна клінічна лікарня ім. І. І. Мечнікова». У дослідження увійшло 30 жінок з OA віком від 40 до 75 років з OA I–III рентгенологічної стадії за Kellgren та Lawrence з явищами синовіту; рівнем болю за візуально-аналоговою шкалою (ВАШ) ≥ 3 бали; ожирінням I–III ступеня (індекс маси тіла – ІМТ 30–49,9 кг/м²) після отримання їх інформованої згоди. Ожиріння серед хворих на OA асоціювалося з тенденцією до вищого рівня болю за ВАШ з боку колінних суглобів. Ступінь рухових обмежень залежно від ІМТ прямо пропорційно збільшувалась з підвищенням ІМТ. Рівень системного запалення у хворих на OA при ожирінні був достовірно вищим. Лікування напроксеником достовірно знижувало рівень лептину незалежно від ожиріння. Використання напроксена натрію (Напрофф) у хворих на OA з явищами синовіту приводить до вираженого знизлювання та протизапального ефекту. Лептин відіграє важливу роль у формуванні інсулінорезистентності та підтриманні незакріпованого запалення при OA у осіб з ожиріннями.

Ключові слова: остеоартрит, ожиріння, адипокін, напроксен натрію.