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Use of diet supplements in older patients

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Abstract

Introduction: Dietary supplements are ingredients in the diet of a growing number of people, especially seniors. The physiological processes of aging of the body are often accompanied by disease processes, which may result in malnutrition of the body and supplement using could be a presumably auxiliary therapy.

Material and Methods: The paper reviews literature using the EBSCO and Google Scholar databases. Articles have been analyzed using the keywords aging, elderly, malnutrition, supplements, vitamins, minerals, supplementation. The article presents effects of the use of individual dietary supplements.

Results: Among the elderly, it would be worth to consider supplementation with vitamins D3, K2, B12. In addition to vitamins, iron, selenium, creatine, leucine, milk thistle, omega 3 acids use could be considered.

Conclusions: Vitamins, microelements and amino acids are essential for the proper functioning of the body, while some groups of elderly are malnutritioned and could gain benefit from diet supplements. Individually prescribed therapy using supplements should be based on deficiencies examination using objective tests, for example blood test.

Key words: aging, elderly, malnutrition, supplements, vitamins, minerals, supplementation.

Introduction

Elderly people constitute the fastest growing population of societies in the developing countries [1]. Ageing is associated with physiological and economical changes that could deteriorate nutritional status [2]. Although undernutrition and lack of nutritional supplements in elderly people are often cited as potentially reversible causes of frailty, morbidity, serious infections, depression, muscle mass loss, bones fractures and falls and injuries, the efficacy of interventions targeted specifically at these deficits has not been carefully studied [3]. A lot of elderly people worldwide take multivitamin and mineral supplements, hoping to promote health, but few studies showed their benefits, which has raised concern in the literature recently. It has been shown that in elderly people, supplementation with different nutrients improves health level.

The aim of the review is to evaluate mineral and nutritional supplements truly necessary in elderly people and exclude those that influence over health is not sufficiently proven [4].

Material and methods

The available literature was subjectively selected due to its usefulness in showing potential risk and benefits of using nutritional supplementation in elderly people. Moreover, literature which reveals inconsistency in results was shown as well. Articles in the EBSCO and the Google Scholar database have been analyzed using keywords: aging, elderly, malnutrition, supplements, vitamins, minerals, diet supplements

Results:

1. Role of vitamin K

Vitamin K is one of the important factors in the work of the body of older people. Vitamin K deficiency, in the elderly, it is caused mainly by disorders of gastrointestinal tract function, reduced bile secretion, liver diseases or due to the use of antibiotics and other drugs.

Vitamin K is a family of vitamins that differ in number of isoprenoid groups (saturated or unsaturated) which join to 2-methyl-1,4-naphthoquinone ring in C3 position. Proteins (VKDPs) dependent on vitamin K in order to become biologically active require carboxylation [5]. The natural forms of vitamin K include: K1 (phylloquinone or filomenadion) synthesized by plants (found in the green leaves of plants) and K2 (menaquinone; MK) is a family of vitamins, where there is from 1 to 13 attached isoprenoid groups (MK-1 to MK -13), occurs in products of animal origin and is produced by bacteria or formed by conversion from vitamin K1 or K2. Menadione (vitamin K3) and esterified menadione (K4) are synthetic forms that act as provitamins [5]. Defining the human need for vitamin K is difficult due to the lack of knowledge about the content of vitamins in various foods and the lack of sensitive methods for assessing the status [7]. There are various data estimating the average body's need for vitamin K. The study [6] revealed that men and women should take 120 and 90 μ g / day. Other studies have reported that older people (> 55 years) should take phoquinone in the range of 80 to 210 μ g / day compared to younger age groups. Authors [5] estimate that the value of vitamin K in the diet should be between 60 and 200 μ g / day.

Table 1. Vitamin K AI Summary, Ages 19 Years and Older. Adapted from: [6].

AI for Men	
19-30 years	120 μg/day of vitamin K
31–50 years	120 μg/day of vitamin K
51–70 years	120 μg/day of vitamin K
> 70 years	120 μg/day of vitamin K

AI for Women	
19–30 years	90 μg/day of vitamin K
31–50 years	90 μg/day of vitamin K
51–70 years	90 μg/day of vitamin K
> 70 years	90 μg/day of vitamin K

Hypoprothrombinemia is a low level of prothrombin or (II factor) blood coagulation and one of the forms of deficiency. Following the formation of thrombin responsible for the conversion of fibrinogen to fibrin is limited. Consequently leads to difficult formation of the clot, it prolongs the bleeding time and increases the risk of internal and external bleeding. Deficiencies may also be caused by antibiotic therapy, antiplatelet drugs, and above all general malnutrition in this geriatric patient population [6].

Recent studies showed the huge role that vitamin K plays in brain physiology. It takes part in the metabolism of sphingolipids and the activation of the biological protein Gas6. Consequently, it can affect the pathogenesis of Alzheimer's disease (AD). Insufficient intake of vitamin K in AD patients comparing to healthy people was reported [8].

Vitamin K deficiencies are a serious and life-threatening condition caused by excessive bleeding, resulting from the decrease in coagulation factors present in the Gla protein. Osteocalcin (MGP) and Gas6 are responsible for the inhibition of arterial calcification, which reduces the risk of atherosclerosis and maintaining bone strength. Long-term deficiencies can contribute to atherosclerosis, osteoporosis and even cancer [9]. Low vitamin levels are not conducive to antibacterial and antifungal.

Vitamin K increases the mineralization of the skeleton through the proteins Gla which provide to reduction bone resorption, induce of osteoclast apoptosis and inhibits of activity and inhibition of osteoblast apoptosis. Vitamin K2 is an antagonist of the Steroid and Xenobiotic Receptor (SXR), which affects the modeling of the expression of a large number of genes that encode extracellular matrix proteins in bone tissue, mainly collagen in osteoblasts. Vitamin K shows activity at the level of genomic regulation and also affects the differentiation of precursor cells towards osteoblasts.

2. Creatine in sarcopenia

The geriatric age is associated with many diseases that result mainly from involutional changes in the body. Sarcopenia refers to a set of symptoms that progress along with the aging, which includes: loss of muscle mass and strength and reduction of skeletal muscle function. The disappearing of motor units occurs gradually from the age of 30, but only after reaching 50 years muscular atrophy is noticeable [10]. Sarcopenia development could be enforced by an inappropriate diet or lifestyle, it also arises as a result of some diseases and medications. The decreasing of muscle mass results mainly from disorders of the mechanisms: biochemical, cellular, molecular and organ processes [11]. Along with the aging process, biosynthesis of proteins and the formation of myofibrils are slowed down, and the processes of apoptosis and decay prevail in the body. Physical activity combined with proper supplementation could contribute to delaying the development of sarcopenia [12]. One of the worth considering ingredients in daily diet is creatine - a naturally occurring substance in 95-98% in the area of human muscle cells. Creatine is formed by the synthesis of three amino acids: arginine, glycine and methionine and plays an important role in physical activity.

Through combining with the rest of the phosphoric acid it is transformed into phosphate, making it an indispensable source of energy. The main role of creatine phosphate is to provide energy that is necessary for the recovery of ATP molecules used during contraction of muscle. Available studies indicate a positive effect of the combination of creatine supplementation with physical exercise, focused both on speed and strength. Increasing the supply of creatine causes an increase in energy potential in muscle cells. Creatine contributes to the acceleration of the process of ATP reconstruction in circumstances of oxygen deprivation, improving anaerobic capacity of muscle [13]. Supplementation with creatine, mainly directly after the use of resistance training in the elderly age, contributes to a significant increase in lean body mass, contributing to the increase of muscle strength and improvement of their regeneration. Special effects of muscle mass increase are noticeable in the case of type II fibers. Systematic physical activity, with resistance in combination with post-workout creatine supplementation, effectively prevents sarcopenia [14].

3. What is more effective in sarcopenia - BCAA or leucine only supplementation?

Protein is one of the six basic components of food for the body and about 20% of the body weight of an adult human as a component of skeletal muscles, the brain, but also the skin, nails, hair, is the main component for enzymes, hormones, or morphotic blood elements. Furthermore, it takes part in the blood coagulation process, immune reactions, blood and tissue buffering, osmotic pressure regulation, but also a biocatalyst and metabolic regulator [15]. Protein, when delivered to the body in the form of food, breaks down in the gastrointestinal tract into peptides, which are then broken down into individual amino acids. The human system is able to synthesize individual amino acids for its own needs, but not all. It is necessary to supply amino acids (endogenous or conditionally unnecessary) could be synthesized by the human body. Branched chain amino acids (BCAA's): valine, leucine and isoleucine [16] constitute 25% of muscle, have anabolic and anti-catabolic properties and participate in the metabolism of fat [17,18].

Leucine, a branched chain aliphatic amino acid, is the source of energy for the body and belongs to an essential amino acids. In the case of deficiencies mechanisms based on aminotransferases in tissues convert α -keto acid to leucine, valine and isoleucine can be presented. Therefore, α -keto acids may be the source of the corresponding amino acids. Muscle cells are sensitive to leucine and react to its elevated concentration due to mammalian Target of Rapamycin (mTOR) kinase which is mainly related to muscle anabolism during and after strength training, however, a certain leucine level should be achieved to activate mTOR [18]. Norton L. et al. suggest that leucine threshold should be at the level of 3.2 to 4.4 g leucine, and other authors showed similar values [19]. After delivering the right amount of leucine to the body, the mTOR kinase is activated, and then the anabolism changes in the muscles. Leucine is contained in animal products: as milk, eggs, cheese and meat. People on a vegetarian or vegan diet should provide these amino acids, supplementing protein supplements.

Glutamine and carnitine are another important amino acids. Glutamine is the main building block of skeletal muscle in the human body. Carnitine deliver muscle acids to the mitochondria which provides to saving glycogen and reducing fat. Increasing muscle mass through protein supplementation results improvement in strength training efficacy. Protein supplements should be valuable with reference to the amino acid composition, primarily branched, and ensure the assimilation of these ingredients. Most protein nutrients are in the form of powders, which should be mixed with water or milk. They are quick to prepare and are an easily digestible source of protein. Another type of nutrients are so-called "Gainer's".

Carbohydrate-protein nutrients, but with a predominance of carbohydrates. In addition, they contain other substances, such as keratin, macro- and micronutrients, produced with special purpose for people doing sports [20].

4. Milk thistle, omega 3- role in HDL/LDL profile?

The milk thistle is a plant and a source of substance called silymarin. This substance has been used as a medicine for centuries. Current studies showed that silymarin helps to maintain a higher high-density lipoprotein cholesterol (HDL-C) level and decrease low-density lipoprotein cholesterol (LDL-C). However, these were studies on the mouse model [21]. Needed further studies to show this effect in humans Further studies on humans are needed.

Omega-3 acids belong to polyunsaturated acids and play an important role in human nutrition, e.i. anticancer activity, reducing cardiovascular risk, improving memory and are helpful in the treatment of rheumatic diseases [22, 23, 24]. Previous studies showed that omega-3 acids reduce hypertriglyceridemia [25]. By contrast, another study showed that the use of omega-3 was associated with higher levels of LDL-C and total cholesterol. However, the authors indicate that the omega-3 levels in patients were low and could not balance other risk factors [26].

5. Vitamin B12, D3, iron, selenium - the role of supplementation in cognitive functions decline in elderly

In spite of many studies on B12 vitamin effects, there is not enough evidence to support the effectiveness of vitamin B12 as a supplement, and the precise mechanism of its effect on cognitive function is still unknown [27].

A commonly recommended supplement is vitamin D. The results of previous studies are inconsistent, however, it is possible to improve mental and physical health during supplementing vitamin D, which may be related to cognitive functioning [28].

High iron levels are associated with cognitive functioning disorders, for example Alzheimer's disease. Therefore, some studies showed that using iron helium compounds, thus leads to reducing iron level. They indicate that reducing iron levels is associated with a decrease in the deterioration of cognitive functioning of patients. In contrast to iron, selenium is an element necessary for the proper functioning of the brain, and its deficiency causes absolute brain damage and, as a result, worse cognitive functioning [29]. Previous studies on

the selenium supplementation showed improving cognitive function, even in patients with mild cognitive impairment [30,31,32].

6. Neuroprotective role of wine, beer and spirits (which one is the best option?) - ethanol or polyphenols?

Despite the many evidence of alcohol-related toxic effects on the nervous system, there are more and more reports of the protective role of ethanol in lower doses. The reason for this phenomenon may be the ability of ethanol to inhibit NMDA-mediated excitotoxicity, occurring during i.a. in traumatic brain injury. Research on animal models showed that small doses of ethanol administered 2 hours after the onset of a trauma leaded to the less brain lesions than those not treated with alcohol [33]. It is worth mentioning the role of alcohol in the prevention of neurodegenerative diseases, including AD. Lower doses of ethanol have been demonstrated to prevent the deposition of β -amyloid, an important factor leading to the development of AD. Their smaller amount delays the onset of Alzheimer's disease symptoms or completely prevents them from happening [34].

Apart from the essential role of ethanol in neuroprotective activity, the type of drink in which we consume ethanol is also important, because of the remaining ingredients that occur in individual drinks. The most important example here is trans-resveratrol, an antioxidant found in several types of red wine. Its consumption could lead to the reduction in incidents of coronary heart diseases, reduce the incidence of neurodegenerative diseases, such as Alzheimer's disease [35]. According to these data, red wine, rich in resveratrol, seems to have greater neuroprotective potential than other alcoholic beverages.

The influence of different types of drinks on the length and quality of life, including the neuroprotective role, has been significantly described in the City Heart Study [37]. In the study participated 13,329 women and men aged 45 to 84, and one of the elements of the study was to determine preferences in consuming alcoholic beverages, and then to compare data with health status. According to the received data, the risk of death decreased with the increase in wine consumption, while there was no lower risk of death in the consumption of beer or spirit. Such a state persisted regardless of sex, age, education, income, smoking, or body mass index [36]. The same study also showed a different neuroprotective role of different types of alcoholic beverages, because it has been shown that consumption of wine significantly reduces the risk of stroke. This role was not observed in the consumption of beer and spirit [37]. Consumption of wine, probably due to the presence of resveratrol [35], is therefore the best option for our health when it comes to alcohol consumption.

Discussion

The evidence for the effectiveness of the routine use of multivitamins in an elderly population to reduce malnutrition and risk of earlier development of serious diseases in adduced researches is of poor to moderate quality, heterogeneous, and conflicting. We can see that every supplement or mineral has quite positive impact for elderly people's health in one or few different ways, but we cannot found unambiguous evidence to prove necessity and dosage of their taking. That is because many of researches about malnutrition and necessity of oral supplementation are still leaded. It is also worth noting that while one studies have been shown positive effects of supplementation, other studies using excessive micronutrient supplements (in larger doses than implemented in any of the trials reviewed here) have been shown to have toxic effects and may impair cellular function [38]. The potential underlying mechanism by which multivitamins and minerals generally and specifically protect health of elderly people is still uncertain. Currently, not enough evidence exists to recommend the routine use of micronutrient supplements for an elderly population. However, the results of the above review are sufficiently encouraging to warrant further and more expansive studies in this area of considerable public health importance [4].

Conclusions

The constantly growing population of older people in the society force to look for new problems of the elderly and to find ways to solve them. One of such problems is malnutrition and a shortage of minerals, vitamins and dietary supplements, which significantly weaken the health of older person and can contribute to the development of complications. Among the dietary components that the necessity of supplementation in the elderly people we have reviewed in scientific articles are: vitamins D3, K2, B12, iron, selenium, creatine, leucine, milk thistle, omega 3 acids. Deficiency of vitamin K2 can lead to hypoprothrombinemia, prolonged bleeding time, external bleeding, earlier occur of nervous system diseases (including Alzheimer's disease), earlier development of atherosclerosis, osteoporosis and even cancers. Lack of creatine and leucine can lead to sarcopenia. Amino acids supplementation and moderate, regular physical activity lead to increase in lean body mass, contributing to the improvement of muscle strength and acceleration of their regeneration. Supplementation of milk thistle can reduce LDL cholesterol level and optimize cholesterol profile, and omega 3 acids reduce hypertriglyceridemia. Supplements which improve cognitive functions in elderly people and slow down their decline are vitamin B12, iron and selenium. Vitamin D3 has a pleiotropic effects that help to maintain mental and physical health, especially to increase build of calcium into the bones and prevent the development of osteoporosis. Improvement of the body's functioning and mental and physical health in the elderly is influenced by a proper, balanced diet, moderate, regular physical activity and proper alignment of nutritional deficiencies with dietary supplements with scientifically proven clinical effectiveness. That is important that for most of the supplements presented in our review, there is a lack of unambiguous scientific evidence indicating the necessity of their supplementation in the daily diet of the elderly. That is why more researches on this subject are necessary and still leaded.

References

1. Gershwin M. E., Hurley, L.: Trace metals and immune function in the elderly. Comprehensive therapy 1987; 13(2): 18-23.

- 2. Bales C. W:. Nutrition, Aging, and the Elderly. Human Nutrition: A Comprehensive Treatise. American Scientist 1991; 79 (6): 566.
- Fiatarone M. A., O'Neill E. F., Ryan N. D., Clements K. M., Solares G. R., Nelson M. E., Evans W. J.: Exercise training and nutritional supplementation for physical frailty in very elderly people. New England Journal of Medicine 1994; 330(25): 1769-1775.
- 4. El-Kadiki A., Sutton A. J.: (2005). Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials. BMJ 2005; 330 (7496): 871.
- 5. Żak-Gołąb A, Okopień B, Chudek J.: Witamina K a metabolizm kości i kalcyfikacja naczyń w przewlekłej chorobie nerek. Przegl. Lek. 2011; 68: 629.
- Trumbo P, Yates A, Schlicker S, Poos M.: Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Journal of the American Dietetic Association 2001; 101(3): 294-301.
- 7. Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. The Journal of nutrition 1998; 128 (5): 785-788.
- 8. Presse N, Shatenstein B, Kergoat J, Ferland G.: Low vitamin K intakes in community-dwelling elders at an early stage of Alzheimer's disease. Journal of the American Dietetic Association 2008; 108 (12): 2095-2099.
- 9. Vermeer C. V.: Vitamin K: the effect on health beyond coagulation–an overview. Food & nutrition research 2012; 56 (1): 5329.
- 10. Candow D. G., Chilibeck P. D.: Effect of creatine supplementation during resistance training on muscle accretion in the erderly. The Journal od Nutrition 2007; 2(11): 185-188.
- 11. Candow D. G., Vogt E., Johannsmeyer S., Forbes S. C., Farthing J. P.: Strategic creatine supplementation and resistance training in healthy older adults. Applied Physiology, Nutrition, and Metabolism 2015; 40 (7): 689-694.
- Dalbo V. J., Roberts M. D., Lockwood C. M., Tucker P. S., Kreider R. B., Kerksick C. M.: The effects of age on skeletal muscle and the phosphocreatine energy system: can creatine supplementation help older adults. Dynamic Medicine 2009; 8 (6): 1-11.
- 13. Candow D. G.: Sarcopenia: current theories and the potential beneficial effect of creatine application. Biogerontology 2011; 12: 273-281.
- 14. Tarnopolsky M., Zimmer A., Paikin J., Safdar A., Aboud A., Pearce E., Roy B., Doherty T.: Creatine Monohydrate and Conjugated Linoleic Acid Improve

Strength and Body Composition Following Resistance Exercise in Older Adults. Plos One 2007; 10: 1-11.

- 15. Murray R., Granner D., Rodwell V.: Biochemia Harpera. Wyd. PZWL 2006; 295-327.
- Zając A., Poprzęcki S., Czuba M.: Dieta i suplementacja w Sporcie I Rekreacji. Wyd. AWF Katowice 2012; 107-126.
- 17. Tomaszewski W.: Żywienie i wspomaganie– kalendarz trenera kulturystyki. Wyd. Medsportpress 1998; 119-126.
- 18. Dymkowska-Malesa M., Walczak Z.: Supplementation in sport. Nowiny Lekarskie 2011; 80 (3): 199-204.
- 19. Kaletha K.: The evaluation of the Kinetic Constans of Enzyme-Catalysed Reaction with the Use of Integrated Rate Equation. Post. Biochem. 1979; 25: 119-139.
- 20. Kraszewski K.: Środki wspomagające w treningu siłowym. Physical education, sport and health culture in contemporary society: a collection of scientific papers 2009; 3: 102-105.
- 21. Ni X., Wang H.: Silymarin attenuated hepatic steatosis through regulation of lipid metabolism and oxidative stress in a mouse model of nonalcoholic fatty liver disease (NAFLD). Am J Transl Res. 2016; 8 (2): 1073-81.
- 22. Augustsson K., Michaud D.S., Rimm E.B.: A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prev 2003, 12 (1), 64-67.
- 23. Harris W.S.: n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr. 1997; 65 (5): 1645-1654.
- 24. Vargová V., Veselý R., Sasinka M., Török C.: Will administration of omega-3 unsaturated fatty acids reduce the use of nonsteroidal antirheumatic agents in children with chronic juvenile arthritis? Cas Lek Cesk. 1998; 137 (21): 651-653.
- 25. Sawada T., Tsubata H., Hashimoto N.: Effects of 6-month eicosapentaenoic acid treatment on postprandial hyperglycemia, hyperlipidemia, insulin secretion ability, and concomitant endothelial dysfunction among newly-diagnosed impaired glucose metabolism patients with coronary artery disease. An open label, single blinded, prospective randomized controlled trial. Cardiovascular Diabetology 2016; 15 (1): 121.
- 26. Proust F., Drescher O., Laouan-Sidi E.A.: Omega-3 polyunsaturated fatty acid profiles and relationship with cardiometabolic risk factors in Cree (Eeyouch) of Northern Québec. Int J Circumpolar Health 2016; 15 (75): 303.

- Lisiecka J., Androsiuk J., Perkowski R., Sokołowski R., Ciesielska N., Nowak K., Kędziora-Kornatowska K. Effect of dietary supplements for improving cognitive functions in the elderly. Gerontologia Polska 2016; 1: 1-9.
- Elisa J. de Koning, Natasja M. van Schoor, Brenda W.J.H. Penninx: Vitamin D supplementation to prevent depression and poor physical function in older adults: Study protocol of the D-Vitaal study, a randomized placebo-controlled clinical trial. BMC Geriatrics 2015; 15:151.
- Aaseth J., Alexander J., Bjørklund G. et al. Treatment strategies in Alzheimer's disease: a review with focus on selenium supplementation. BioMetals 2016; 29 (5): 827-839.
- 30. Cardoso B.R., Roberts B.R., Bush A.I., Hare D.J.: Selenium, selenoproteins and neurodegenerative diseases. Metallomics 2015; 7: 1213–1228.
- 31. Kesse-Guyot E.: French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the supplementation in vitamins and mineral antioxidants. Am J Clin Nutr 2011; 94: 892–899.
- 32. Scheltens P. et al. Efficacy of a medical food in mild Alzheimer's disease: a randomized, controlled trial. Alzheimers Dement 2010; 6 (1–10): e11.
- 33. Türeci E., Dashti R., Tanriverdi T., Sanus G. Z., Öz B., Uzan M.: Acute ethanol intoxication in a model of traumatic brain injury: The protective role of moderate doses demonstrated by immunoreactivity of synaptophysin in hippocampal neurons. A Journal of Progress in Neurosurgery, Neurology and Neurosciences 2004; 26 (1): 108-112.
- Collins M. A., Neafsey E. J., Wang K., Achille N. J., Mitchell R. M., Sivaswamy S.: Moderate Ethanol Preconditioning of Rat Brain Cultures Engenders Neuroprotection Against Dementia-Inducing Neuroinflammatory Proteins: Possible Signaling Mechanisms. Molecular Neurobiology 2010; 41 (2-3): 420-425.
- 35. Virgili M., Constestabile A.: (2000). Partial neuroprotection of in vivo excitotoxic brain damage by chronic administration of the red wine antioxidant agent, trans-resveratrol in rats. Neuroscience Letters 2000; 281(2-3): 123-126.
- Gronbaek M., Deis A., Sorensen T. I. A., Becker U., Schnohr P., Jensen G.: Mortality associated with moderate intakes of wine, beer, or spirits. British Medical Journal 1995; 310: 1165.
- 37. Truelsen T., Gronbaek M., Schnohr P., Boysen G.: Intake of Beer, Wine, and Spirits and Risk of Stroke. Stroke 1998; 29: 2467-2472.

 Goodwin J. S., Garry P. J.: (1983). Relationship between megadose vitamin supplementation and immunological function in a healthy elderly population. Clinical and experimental immunology 1983; 51 (3): 647.