БИОГЕРОНТОЛОГИЯ

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VITAMIN D AND CARDIOVASCULAR DISEASES

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In recent years increasing information has been published regarding the pleiotropic effects of vitamin D that has long been regarded as a factor playing a role in calcium level regulation and the skeletal system only. The way of life characteristic of present population, with most of the time spent indoors, creates conditions favoring long-term vitamin D deficit, starting in the years compulsory school attendance already. The main source of vitamin D for the human body is solar radiation. This accounts for 80% of the active vitamin supply, while nutrition provides only the remaining 20%, and according to some sources this ratio is even 90% to 10%. This is the reason for the inconsistency of the results of studies based on the evaluation of vitamin D intake in nutrition.

Key words: vitamin D, solar radiation, calcium level regulation.

ВИТАМИН D И СЕРДЕЧНО-СОСУДИСТЫЕ ЗАБОЛЕВАНИЯ

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В последние годы увеличивается количество информации касательно плейотропных эффектов витамина D, который уже давно рассматривается в качестве фактора, играющего роль в регуляции уровня кальция и костной системы. Образ жизни, характерный для населения, большую часть времени проводящего в помещении, создает условия, благоприятные для долгосрочного дефицита витамина Д, начиная уже с лет обязательного школьного обучения.

Основным источником витамина D для человеческого организма является синтез под действием солнечного излучения. Это составляет 80% активного витамина, а питание обеспечивает только оставшиеся 20%, а по некоторым данным это соотношение - 90% и 10%. Именно по этой причине наблюдается несоответствие результатов исследований, основанных на оценке потребления витамина D в питании.

Ключевые слова: витамин D, солнечная радиация, регулирования уровня кальция.

Introduction

In recent years increasing information has been published regarding the pleiotropic effects of vitamin D that has long been regarded as a factor playing a role in calcium level regulation and the skeletal system only. The breakthrough was the information that vitamin D receptors (VDRs) have been identified in most human cells and organs. VDR is a nuclear receptor that is activated after binding of dihydroxycholecalciferol, the active form vitamin D. Insufficient receptor activation caused by low vitamin D level may result in many metabolic, immunologic, cardiovascular and other disturbances [1, 2, 3].

The way of life characteristic of present population, with most of the time spent indoors, creates conditions favoring long-term vitamin D deficit, starting in the years compulsory school attendance already. The main source of vitamin D for the human body is solar radiation that causes the formation of cholecalciferol in the skin that is later then metabolized in the liver to the active 1,25-dihydroxycholecalciferol. This accounts for 80% of the active vitamin supply, while nutrition provides only the remaining 20%, and according to some sources this ratio is even 90% to 10% [4]. This is the reason for the inconsistency of the results of studies based on the evaluation of vitamin D intake in nutrition [5]. It is the very lack of solar radiation that is the most likely cause of the finding that the Czech population, according to first testing results, have vitamin D levels at the border between 30 and 40 mmol/l, the normal range being 50-200 mmol/l, meaning that almost half of the population does not reach levels necessary for good-quality bone remodeling, and, as is gradually becoming clear, also for the normal functioning of a number of other systems [6].

Geographical regions north of 42 degree latitude provide radiation intensity that is insufficient for vitamin D synthesis over the period from November to February, while the interval of insufficient exposure is up to 6 months a year in the regions farther north. Overcast sky reduces the radiation intensity by 50%. The use of creams with UV protection factors above 8 results in an effective blockade of UVB component of solar radiation. In the temperate zone, sufficient vitamin D supply should be ensured with a 10% exposure of whole body unprotected skin surface for 20 minutes between 10 a.m. and 3 p.m., twice a week [7, 8].

Mechanism of cardiovascular system damage associated with vitamin D deficiency.

Long-term follow-up of a sample of 10,000 subjects aiming at revealing the relationships of vitamin D-related cardiovascular damage found that low vitamin D level was associated with significantly higher occurrence rates of hypertension, coronary damage, cardiomyopathy, but also diabetes mellitus. Vitamin D was also a significant predictor of the overall mortality. Vitamin D supplementation resulted in significantly improved survival, especially in patients with demonstrated deficit [9].

In the population of 2,312 elderly patients a group of 384 patients was found with significantly reduced vitamin D level and significantly increased parathormone activity. An analysis of the occurrence of cardiovascular complications demonstrated that every 25-mmol/l reduction of vitamin D level was associated with a 9% increase in mortality and a 25% increase in the risk of myocardial infarction. Parathormone values higher than 65ng/l were associated with a 30% increase of cardiac failure risk [10].

Regarding the possible mechanisms of cardiovascular damage due to long-term low vitamin D levels the analogy with the mice model where the animals deprived of vitamin D receptors developed cardiovascular damage more rapidly as a result of accelerated atherosclerosis, increased inflammatory reaction and increased parathormone level. Vitamin D supplementation was associated with anti-sclerotic, anti-inflammatory, direct cardioprotective and parathormone suppressive effects [1].

Similar results were obtained in cross-sectional studies in cardiac patients where a correlation analysis demonstrated a significant negative (inverse) relationship between vitamin D level and inflammatory activity, oxidative stress, or the presence of vascular and intercellular adhesive molecules [11].

One possible line of action of vitamin D is interference of the activated vitamin D receptor with the renin-angiotensin-aldosterone system (RAAS), with the subsequent consequence of reduced blood pressure [12]. Vitamin D deficiency resulted in RAAS activation with vasoconstriction, sodium and water retention, and increased arterial wall rigidity [14].

Another of the mechanisms of action of vitamin D considered is its influence on calcium metabolism. Decreasing vitamin D levels result in reduced serum calcium level and increased blood pressure, and vice versa. Long-lasting reduced vitamin D level was associated with higher occurrence of strokes [13].

Vitamin D is vital for the synthesis of contractile proteins in the myocardiocyte where it also activates basic intracellular mechanisms of calcium metabolism and energy production as factors that participate in the creation of appropriate myocardial ventricle geometry and efficient myocardial activity [15]. Vitamin D is also important for the regulation of expression of genes coding cytokine and hormone synthesis that participate in the pathogenesis of cardiac failure – natriuretic peptide, the already mentioned renin, as well as other factors [16].

Another structure that might be influenced by reduced vitamin D levels is the cardiac valvular apparatus. Vitamin D deficiency results in reduced calcium levels and increases phosphate levels. A study that included almost 2,000 subjects free of cardiac damage investigated with echocardiography demonstrated that every increase of serum phosphate in steps of 50mmol/l was associated with increased risk of aortic valve atherosclerosis and development of calcifications in the aortic and mintral annuli. These relationships, however, concerned only the levels of phosphorus, while neither calcium and vitamin D levels nor parathormone levels showed the described relationship [17].

Vitamin D and coronary artery disease.

Numerous studies have demonstrated a significant relationship between low vitamin D levels and the degree of seriousness of both acute and chronic forms of coronary artery disease. For example, vitamin D level follow-up in patients who were indicated for coronary artery interventional procedures has shown that patients with low vitamin D level had significantly increased risk of cardiac failure and sudden cardiac death in their further course compared to patients with vitamin D levels in the normal range [18]. Another study compared the occurrence rate and course of coronary artery disease after the patients underwent coronary intervention. Patients with demonstrated coronary artery disease had vitamin D levels that were overall significantly lower than in the control group, and detailed analysis according to actual vitamin D levels showed a 2.5 times higher coronary artery risk in patients in the first (lower) quartile as compared with those in the last (upper) quartile. The study has also demonstrated a significant inverse relationship between the level of vitamin D on the one hand and triglyceride levels, BMI and bodily weight on the other, and vegetarians were found to have significantly lower vitamin D levels [19]. The conclusions of this study provide an independent confirmation of the results of a multicenter vitamin D level follow-up in patients who had already sustained myocardial infarction, where 96% of these patients were found to have vitamin D lever that were lower the then normal range [20].

In the case of an already developed cardiac failure a vicious circle sets in where reduced patient mobility results in lower skin exposure to solar radiation and thus in further reductions of vitamin D levels (Szabó). The greatest positive gain of vitamin D supplementation may be expected in the group of patients with serum levels below 50-70 mmol/l (Patel). This patient group has also the highest mortality rates and risk of repeated hospital stay for recurrent cardiac decompensation [23].

The relationship with low serum vitamin D levels is reported by many authors, and the pathogenesis of both acute and chronic forms has been described to depend on mechanisms influencing the synthesis of the natriuretic peptide, contractility, the renin-angiotensin-aldosterone system, on endothelial function, on the activity of inflammatory response, and increased blood pressure, but most of these authors also point to the lack of prospective interventional studies that would demonstrate an effect of vitamin D supplementation on improved prognosis, and call for such studies to be carried out [21, 18, 16, 24, 11, 25]. Based on the evidence supporting the effect of vitamin D, however, some authors do recommend already now that the therapy of all forms of coronary artery disease consider the serum level of vitamin D, and when this is found to be reduced, that the treatment schedule be extended to include a preparation ensuring vitamin D supply [16, 26].

Vitamin D and dyslipidemia.

Direct influence of vitamin D on the level of cholesterol has not been reliably demonstrated, not even an indirect one, through the anticipated mutual interaction with statins. In patients with renal failure, however, a positive influence of vitamin D on the reduction of triglyceride level has been found [27]. From the viewpoint of vascular damage, the effect of vitamin D appears to be two-phase – the damage occurs with very low, but also with very high levels.

Vitamin D and arrhythmia.

Regarding the ever more obvious relationships between vitamin D and cardiovascular system function attention has also been paid to the possibility of a possible relationship with the increasing occurrence of atrial fibrillation. As part of the Framingham study a group of almost 3,000 individuals with mean age 65 years has been followed-up for nine years regarding the incidence of newly developed atrial fibrillation. A multivariate analysis failed to demonstrate a relationship between vitamin D level and the risk of atrial fibrillation [28]. On the other hand, it is necessary to consider the mutual relationship of vitamin D and maintenance of stable serum calcium or magnesium levels, that are known as important

cardiac rhythm stabilizers [29]. It has also been shown that higher serum parathormone levels provoked by low vitamin D levels are associated with negative impact. Receptor binding results in the stimulation of phospholipase C, with subsequent increase of the activities of catecholamine, angiotensin II and endothelin, with possible arrhythmogenic activity in the ischemic myocardium [30]. The study NHANES as well has confirmed, in a sample of 37 thousand subjects, and as a secondary finding, significant influence of low vitamin D level on increased pulse rate and systolic blood pressure, with subsequent increase of myocardial oxygen consumption, and ensuing deepening of ischemia in an already present coronary damage [31].

Vitamin D and hypertension.

The relationship between vitamin D and blood pressure has also been explained through the mediation of the renin–angiotensin system, and through its effect on parathormone secretion, and the anti-inflammatory and vasculoprotective effects of vitamin D. Low vitamin D levels were associated with blood pressure increase by 2-6 mmHg, and low levels have been shown to be an independent risk factor for hypertension. Regarding the high occurrence rates of both hypertension and vitamin D deficiency in the elderly population it is possible to consider the possibility of positive modulation of antihypertensive therapy with maintaining vitamin D levels in the normal range [32].

Another possible mechanism underlying the development of increased blood pressure in vitamin D insufficiency is the increased aortic rigidity demonstrated recently by Czech authors in subjects with reduced serum levels of 25-hydroxyvitamin D, independently of age and gender [33]. Still another possible explanations for the contribution of vitamin D to blood pressure control are the already demonstrated factors such as endothelial dysfunction, increased tendency to vascular and myocardial cell calcification and higher inflammatory activity associated with low vitamin D levels [34].

Conclusion

The pleiotropic effects of vitamin D should be extended to include also the positive influence of physiological vitamin D levels on the cardiovascular system.

Maintaining the vitamin D level in the normal range might positively influence the therapy of coronary artery disease, arterial hypertension, arrhythmias and also cardiac failure.

The exposure to solar radiation is more important for the maintenance of sufficient vitamin D levels than vitamin D intake in foods.

References.

1. Pilz S. Vitamin D cardiovascular disease and mortality / S. Pilz, A. Tomaschitz, W. März [et al.] // Clin Endocrinol (Oxf). – 2011. – Vol. 75, № 5. – P. 575 - 584.

2. Wu-Wong Jr. Vitamin D therapy in cardiac hypertrophy and heart failure / Jr. Wu-Wong // Curr Pharm Des. – 2011. – Vol. 17, № 18. – P. 1794 - 1807.

3. Holick J.R. Vitamin D: ad-lightful solution for health / J.R. Holick // J Investig Med. - 2011. – Vol. 59, № 6. – P. 872 - 80.

4. Heine G. 1 - alpha, 25-dihydroxyvitamin D3 inhibits anti CD40 plus IL-4 mediated IgE production in vitro / G. Heine, K. Anton, B.M. Henz [et al.] // Eur J Immunol. – 2002. – № 32. – P. 3395 - 3404.

5. Sun Q. Vitamin D intake and risk of cardiovascular disease in US men and women / Q. Sun, L. Shi, E.B. Rimm [et al.] // Am J Clin Nutr. - 2011. – Vol. 94, № 2. – P. 534 - 542.

6. Kubešová H. M. Problematika vitaminu D u seniorů // Gerontologický kongres Hradec Králové: sborník abstrakt. (prosinec 2010). - Hradec Králové, 2010.

7. Dietary suplement sheet: Vitamin D / Office of Dietary Supplements. National Institute of Health, 2011. P. 1 – 15.

8. Vyskočil V. Vitamin D. / V. Vyskočil // Klinická farmakologie a farmacie. – 2011. – Vol. 25, № 2. - P. 72 - 75.

9. Vacek J.L. Vitamin D Deficiency and Supplementation and Relation to Cardiovascular Health / J.L Vacek, S.R. Vanga, M. Good [et al.] // Am J Cardiol. – 2012. – Vol. 109, № 3. - P. 359 – 363.

10. Kestenbaum B. Vitamin D, parathyroid hormone, and cardiovascular events among older adults / B. Kestenbaum , R . Katz , I. de Boer [et al.] // J Am Coll Cardiol. - 2011. – Vol. 58, № 14. - P. 1433 - 1141.

11. Dobnig H. Independent association of low serum 25-hydroxyvitamin d and 1, 25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality / H. Dobnig, S. Pilz, H. Scharnagl, W. Renner [et al.] // Arch Intern Med. - 2008. – Vol. 58, № 2. – P. 1340 - 1349.

12. Schroten N.F. New roles for renin and prorenin in heart failure and cardiorenal crosstalk / N.F. Schroten, C.A. Gaillard, D.J. van Veldhuisen [et al.] // Heart Fail Rev. – 2012. – Vol. 17, № 2. – P. 191 – 201.

13. Guessous I. Calcium, vitamin D and cardiovascular disease / I. Guessous, M. Bochud, O. Bonny [et al.] // Kidney Blood Press Res. - 2011. – Vol. 34, № 6. – P. 404 - 417.

14. Cozzolino M. The impact of paricalcitol on left ventricular hypertrophy / M. Cozzolino, C. Ronco // Contrib Nephrol. - 2011. – №. 171. – P. 161 - 165.

15. Cioffi G. Vitamin D deficiency, left ventricular dysfunction and heart failure / G. Cioffi, D. Gatti, S. Adami // G Ital Cardiol (Rome). - 2010. – Vol. 11, № 9. – P. 645 - 653.

16. Meems L.M. Vitamin D biology in heart failure: molecular mechanisms and systematic review / L.M. Meems, P. van der Harst, W.H. van Gilst, R.A. de Boer // Curr Drug Targets. – 2011. – Vol. 12, № 1. – P. 29 - 41.

17. Linefsky J.P. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study / J.P. Linefsky, K.D. O'Brien, R. Katz [et al.] // J Am Coll Cardiol. - 2011. – Vol. 58, № 3. – P. 291 - 297.

18. Pilz S. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross - sectional study of patients referred for coronary angiography/ S. Pilz, W. März, B. Wellnitz [et al.] // J Clin Endocrinol Metab. - 2008. – Vol. 93, № 10. – P. 3927 - 3935.

19. Shanker J. Role of vitamin D levels and vitamin D receptor polymorphisms in relation to coronary artery disease: the Indian atherosclerosis research study / J. Shanker, A. Maitra, P. Arvind [et al.] // Coron Artery Dis. - 2011. – Vol. 22, № 5. – P. 324 - 332.

20. Lee J.H. Prevalence of vitamin D deficiency in patients with acute myocardial infarction /J.H. Lee, R. Gadi, J.A. Spertus [et al.] // Am J Cardiol. - 2011. – Vol. 107, № 11. – P. 1636-1638.

21. Szabó B. The role of vitamin D in the development of cardiac failure / B Szabó, B Merkely, I. Takács // Orv Hetil. - 2009. – Vol. 150, № 30. – P. 1397 - 1402.

22. Patel R. Vitamin D deficiency in patients with congestive heart failure: mechanisms, manifestations, and management / R. Patel, AA. Rizvi // South Med J. - 2011. – Vol. 104, № 5. – P. 325 - 330.

23. Liu L.C. Vitamin D status and outcomes in heart failure patients / L.C. Liu, A.A. Voors, D.J. van Veldhuisen [et al.] // Eur J Heart Fail. - 2011. – Vol. 13, № 6. – P. 619 - 625.

24. Witham M.D. Vitamin D in chronic heart failure / M.D. Witham // Curr Heart Fail Rep. - 2011. – Vol. 8, № 2. – P. 123 - 130.

25. Grandi N.C.Vitamin D and cardiovascular disease: systematic review and meta - analysis of prospective studies / N.C. Grandi, L.P. Breitling, H. Brenner // Prev Med. - 2010. – Vol. 51, № 3-4. – P. 228 - 233.

26. Pilz S. Vitamin D deficiency and myocardial diseases / S. Pilz, A Tomaschitz, C. Drechsler, J.M. Dekker, W. März // Mol Nutr Food Res. - 2010. – Vol. 54, № 8. – P. 1103 - 1113.

27. Zittermann A. The role of vitamin d in dyslipidemia and cardiovascular disease / A. Zittermann, J.F. Gummert, J. Börgermann // Curr Pharm Des. - 2011. – Vol. 17, № 9. – P. 933 - 942.

28. Rienstra M.Vitamin D status is not related to development of atrial fibrillation in the community / M. Rienstra, S. Cheng, M.G. Larson // Am Heart J. 2011. – Vol. 162, № 3. – P. 538 - 541.

29. Bobkowski W. The importance of magnesium status in the pathophysiology of mitral valve prolapse / W Bobkowski, A. Nowak // Cardiol Rev. 2012. – Vol. 20, № 1. – P. 38 - 44.

30. McCarty M.F. Can moderate elevations of parathyroid hormone acutely increase risk for ischemic cardiac arrhythmias? / M.F. McCarty, J. Barroso – Aranda, F. Contreras // Med Hypotheses. - 2009. – Vol. 72, № 5. – P. 581 - 583.

31. Scragg R.K. Relation of serum 25-hydroxyvitamin D to heart rate and cardiac work (from the National Health and Nutrition Examination Surveys) / R.K. Scragg, C.A. Jr. Camargo, R.U. Simpson // Am J Cardiol. - 2010. – Vol. 105, № 1. – P. 122 - 128.

32. Pilz S. Role of vitamin D in arterial hypertension / S. Pilz, A. Tomaschitz // Expert Rev Cardiovasc Ther. – 2010. – Vol.8, № 11. – P. 1599 - 1608.

33. Mayer O. Jr. The association between low 25-hydroxyvitamin D and increased aortic stiffness / O. Jr. Mayer, J. Filipovský, J. Seidlerová [et al.] // J Hum Hypertens. - 2012. – Vol. 26, № 11. – P. 650 - 655.

34. Liss Y. Vitamin D: a cardioprotective agent? / Y. Liss , W.H. Frishman // Cardiol Rev. - 2012. – Vol. 20, № 1. – P. 38 - 44.

References.

1. Pilz S., Tomaschitz A., März W. [et al.] *Clin Endocrinol (Oxf).* 2011, Vol. 75, no. 5, pp. 575 - 584.

2. Wu-Wong Jr. *Curr Pharm Des.* 2011, Vol. 17, no. 18, pp. 1794 - 1807.

3. Holick J.R. *J Investig Med.* 2011, Vol. 59, no. 6, pp. 872 - 80.

4. Heine G., Anton K., Henz B.M. [et al.] *Eur J Immunol*. 2002, no. 32, pp. 3395 - 3404.

5. Sun Q., Shi L., Rimm E.B. [et al.] *Am J Clin Nutr.* 2011, Vol. 94, no. 2, pp. 534 - 542.

6. Kubešová H. M. *Problematika vitaminu D u seniorů.* Hradec Králové, 2010.

7. *Dietary suplement sheet: Vitamin D* National Institute of Health, 2011. P. 1 – 15.

8. Vyskočil V. *Klinická farmakologie a farmacie.* 2011, Vol. 25, no. 2, pp. 72 - 75.

9. Vacek J.L., Vanga S.R., Good M. [et al.] *Am J Cardiol.* 2012, Vol. 109, no. 3, pp. 359 – 363.

10. Kestenbaum B, Katz R., de Boer I. [et al.] *J Am Coll Cardiol.* 2011, Vol. 58, no. 14, pp. 1433 - 1141.

11. Dobnig H., Pilz S., Scharnagl H., Renner W. [et al.] *Arch Intern Med.* 2008, Vol. 58, no. 2, pp. 1340 - 1349.

12. Schroten N.F., Gaillard C.A., van Veldhuisen D.J. [et al.] *Heart Fail Rev.* 2012, Vol. 17, no. 2, pp. 191 – 201.

13. Guessous I., Bochud M., Bonny O. [et al.] *Kidney Blood Press Res.* 2011, Vol. 34, no. 6, pp. 404 - 417.

14. Cozzolino M., Ronco C. *Contrib Nephrol.* 2011, no. 171, pp. 161 - 165.

15. Cioffi G., Gatti D., Adami S. G *Ital Cardiol (Rome).* 2010, Vol. 11, no. 9, pp. 645 - 653.

16. Meems L.M., van der Harst P., van Gilst W.H., de Boer R.A. *Curr Drug Targets.* 2011, Vol. 12, no. 1, pp. 29 - 41.

17. Linefsky J.P., O'Brien K.D., Katz R. [et al.] *J Am Coll Cardiol.* 2011,Vol. 58, no. 3, pp. 291 - 297.

18. Pilz S., März W., Wellnitz B. [et al.] *J Clin Endocrinol Metab*. 2008,Vol. 93, no. 10, pp. 3927 - 3935.

19. Shanker J., . Maitra A., Arvind P. [et al.] *Coron Artery Dis.* 2011, Vol. 22, no. 5, pp. 324 - 332.

20. Lee J.H., Gadi R., Spertus J.A. [et al.] // *Am J Cardiol.* 2011, Vol. 107, no. 11, pp. 1636-1638.

21. Szabó B., Merkely B, Takács I. *Orv Hetil.* 2009, Vol. 150, no. 30, pp. 1397 - 1402.

22. Patel R., Rizvi AA. *South Med J*. 2011, Vol. 104, no. 5, pp. 325 - 330.

23. Liu L.C., Voors A.A., van Veldhuisen D.J. [et al.] *Eur J Heart Fail.* 2011, Vol. 13, no. 6, pp. 619 - 625.

24. Witham M.D. *Curr Heart Fail Rep*. 2011, Vol. 8, no. 2, pp. 123 - 130.

25. Grandi N.C., Breitling L.P., Brenner H. *Prev Med.* 2010, Vol. 51, no. 3-4, pp. 228 - 233.

26. Pilz S., Tomaschitz A., Drechsler C., Dekker J.M., März W. *Mol Nutr Food Res.* 2010, Vol. 54, no. 8, pp. 1103 - 1113.

27. Zittermann A., Gummert J.F., Börgermann J. *Curr Pharm Des.* 2011, Vol. 17, no. 9, pp. 933 - 942.

28. Rienstra M., Cheng S., Larson M.G. *Am Heart J.* 2011. Vol. 162, no. 3, pp. 538 - 541.

29. Bobkowski W, Nowak A. *Cardiol Rev.* 2012, Vol. 20, no.1, pp. 38 - 44.

30. McCarty M.F., Barroso – Aranda J., Contreras F. *Med Hypotheses.* 2009,Vol. 72, no. 5, pp. 581 - 583.

31. Scragg R.K., Camargo C.A. Jr., Simpson R.U. *Am J Cardiol.* 2010, Vol. 105, no. 1, pp. 122 - 128.

32. Pilz S., Tomaschitz A. *Expert Rev Cardiovasc Ther.* 2010, Vol.8, no. 11, pp. 1599 - 1608.

33. Mayer O. Jr., Filipovský J., Seidlerová J. [et al.] *J Hum Hypertens.* 2012, Vol. 26, no. 11, pp. 650 - 655.

34. Liss Y., FrishmanW.H. *Cardiol Rev.* 2012, Vol. 20, no. 1, pp. 38 - 44.