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ЗА ПРИСЪЖДАНЕ НА АКАДЕМИЧНАТА ДЛЪЖНОСТ „ДОЦЕНТ“

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1. **Kostov K,** Blazhev A, Atanasova M, Dimitrova A. Serum Concentrations of Endothelin-1 and Matrix Metalloproteinases-2, -9 in Pre-Hypertensive and Hypertensive Patients with Type 2 Diabetes. International Journal of Molecular Sciences. 2016, 17(8), 1182. ISSN: 1422-0067, **Web of Science Q2 IF$_{2016}$ 3.226, Scopus Q1 SJR$_{2016}$ 1.235**

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Article

Serum Concentrations of Endothelin-1 and Matrix Metalloproteinases-2, -9 in Pre-Hypertensive and Hypertensive Patients with Type 2 Diabetes

Krasimir Kostov [1,*], Alexander Blazhev [2], Milena Atanasova [2] and Anelia Dimitrova [1]

1 Department of Physiology and Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; anelija.dimitrova@gmail.com
2 Division of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; yalishanda9@gmail.com (A.B.); milenaar2001@yahoo.com (M.A.)
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

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Abstract: Endothelin-1 (ET-1) is one of the most potent vasoconstrictors known to date. While its plasma or serum concentrations are elevated in some forms of experimental and human hypertension, this is not a consistent finding in all forms of hypertension. Matrix metalloproteinases -2 and -9 (MMP-2 and MMP-9), which degrade collagen type IV of the vascular basement membrane, are responsible for vascular remodeling, inflammation, and atherosclerotic complications, including in type 2 diabetes (T2D). In our study, we compared concentrations of ET-1, MMP-2, and MMP-9 in pre-hypertensive (PHTN) and hypertensive (HTN) T2D patients with those of healthy normotensive controls (N). ET-1, MMP-2, and MMP-9 were measured by ELISA. Concentrations of ET-1 in PHTN and N were very similar, while those in HTN were significantly higher. Concentrations of MMP-2 and MMP-9 in PHTN and HTN were also significantly higher compared to N. An interesting result in our study is that concentrations of MMP-2 and MMP-9 in HTN were lower compared to PHTN. In conclusion, we showed that increased production of ET-1 in patients with T2D can lead to long-lasting increases in blood pressure (BP) and clinical manifestation of hypertension. We also demonstrated that increased levels of MMP-2 and MMP-9 in pre-hypertensive and hypertensive patients with T2D mainly reflect the early vascular changes in extracellular matrix (ECM) turnover.

Keywords: pre-hypertension; type 2 diabetes; endothelin-1; matrix metalloproteinases-2; matrix metalloproteinases-9; vascular remodeling

2. **Kostov K,** Halacheva L. Role of Magnesium Deficiency in Promoting Atherosclerosis, Endothelial Dysfunction, and Arterial Stiffening as Risk Factors for Hypertension. International journal of molecular sciences. 2018; 19(6): 1724. ISSN: 1422-0067, **Web of Science Q2 IF_{2018} 4.183, Scopus Q1 SJR_{2018} 1.312**

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Review

Role of Magnesium Deficiency in Promoting Atherosclerosis, Endothelial Dysfunction, and Arterial Stiffening as Risk Factors for Hypertension

Krasimir Kostov [1,*] and Lyudmila Halacheva [2]

[1] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria
[2] Department of Physiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; l_halacheva@abv.bg
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

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Abstract: Arterial hypertension is a disease with a complex pathogenesis. Despite considerable knowledge about this socially significant disease, the role of magnesium deficiency (MgD) as a risk factor is not fully understood. Magnesium is a natural calcium antagonist. It potentiates the production of local vasodilator mediators (prostacyclin and nitric oxide) and alters vascular responses to a variety of vasoactive substances (endothelin-1, angiotensin II, and catecholamines). MgD stimulates the production of aldosterone and potentiates vascular inflammatory response, while expression/activity of various antioxidant enzymes (glutathione peroxidase, superoxide dismutase, and catalase) and the levels of important antioxidants (vitamin C, vitamin E, and selenium) are decreased. Magnesium balances the effects of catecholamines in acute and chronic stress. MgD may be associated with the development of insulin resistance, hyperglycemia, and changes in lipid metabolism, which enhance atherosclerotic changes and arterial stiffness. Magnesium regulates collagen and elastin turnover in the vascular wall and matrix metalloproteinase activity. Magnesium helps to protect the elastic fibers from calcium deposition and maintains the elasticity of the vessels. Considering the numerous positive effects on a number of mechanisms related to arterial hypertension, consuming a healthy diet that provides the recommended amount of magnesium can be an appropriate strategy for helping control blood pressure.

Keywords: magnesium deficiency; arterial hypertension; vascular tone; arterial stiffness; vascular remodeling; insulin resistance; magnesium supplementation; dietary magnesium intake

1. Introduction

Magnesium (Mg^{2+}) is the fourth most common mineral in the human body after calcium (Ca^{2+}), potassium (K^{+}), and sodium (Na^{+}), and should be continuously replenished by food and water intake [1]. Mg^{2+} is the second richest intracellular cation after K^{+} and is a cofactor in more than 325 enzyme systems in cells [2]. Mg^{2+} is abundant in all green leafy vegetables, cereal, nuts, and legumes. Chocolate products, fruits, meat, and fish contain moderate amounts of Mg^{2+}, and dairy products are low in Mg^{2+}. Drinking water can be an important source of Mg^{2+} when it contains up to 30 mg/L of Mg^{2+} [3]. Chronic inadequate intake of Mg^{2+} over a long period of time can manifest as latent magnesium deficiency (MgD) [1]. Chronic MgD is associated with an increased risk of multiple preclinical and clinical manifestations including hypertension (HTN), atherosclerosis, cardiac arrhythmias, stroke, changes in lipid metabolism, insulin resistance, metabolic syndrome (MetS), type 2 diabetes (T2D), osteoporosis, depression, and other neuropsychiatric disorders [4] (Table 1). The assessment of Mg^{2+} status in the body is difficult because most is found in the cells or in the bones. Only 1% of the total Mg^{2+} in the body is present

3. **Kostov K**, Blazhev A. Use of Glycated Hemoglobin (A1c) as a Biomarker for Vascular Risk in Type 2 Diabetes: Its Relationship with Matrix Metalloproteinases-2,-9 and the Metabolism of Collagen IV and Elastin. Medicina. 2020; 56(5): 231. ISSN: 1010-660X, **Web of Science Q2 IF_{2020} 2.430, Scopus Q3 SJR_{2020} 0.53**

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Article

Use of Glycated Hemoglobin (A1c) as a Biomarker for Vascular Risk in Type 2 Diabetes: Its Relationship with Matrix Metalloproteinases-2, -9 and the Metabolism of Collagen IV and Elastin

Krasimir Kostov [1,*] and Alexander Blazhev [2]

[1] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria
[2] Department of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; yalishanda9@gmail.com
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

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Abstract: *Background and objectives*: HbA1c measurements may be useful not only in optimizing glycemic control but also as a tool for managing overall vascular risk in patients with diabetes. In the present study, we investigate the clinical significance of HbA1c as a biomarker for hyperglycemia-induced vascular damages in type 2 diabetes (T2D) based on the levels of matrix metalloproteinases-2, -9 (MMP-2, MMP-9), anti-collagen IV (ACIV), and anti-elastin (AE) antibodies (Abs) IgM, IgG, and IgA, and CIV-derived peptides (CIV-DP) reflecting collagen and elastin turnover in the vascular wall. The aim is to show the relationship of hyperglycemia with changes in the levels of vascular markers and the dynamics of this relationship at different degrees of glycemic control reported by HbA1c levels. *Materials and Methods*: To monitor elastin and collagen IV metabolism, we measured serum levels of these immunological markers in 59 patients with T2D and 20 healthy control subjects with an ELISA. *Results*: MMP-2, MMP-9, and the AEAbs IgA levels were significantly higher in diabetic patients than in control subjects, whereas those of the AEAbs IgM, ACIVAbs IgM, and CIV-DP were significantly lower. MMP-9 levels were significantly lower at HbA1c values >7.5%. *Conclusions*: A set of three tested markers (MMP-2, MMP-9, and AEAbs IgA) showed that vascular damages from preceding long-term hyperglycemia begin to dominate at HbA1c values ≥7.5%, which is the likely cut-point to predict increased vascular risk.

Keywords: type 2 diabetes; hemoglobin A1c; matrix metalloproteinases-2 and -9; anti-elastin antibodies; anti-collagen IV antibodies; diabetic retinopathy; diabetic nephropathy; macrovascular complications

1. Introduction

The prevalence of type 2 diabetes (T2D) is increasing worldwide, and it is expected to affect over 500 million adults worldwide by 2030 [1]. T2D is an important contributor to adverse cardiovascular complications, which are the leading causes of morbidity and mortality in Western countries [2].

Prevention of complications in T2D is closely linked to long-term control of hyperglycemia [3] since metabolic consequences extending beyond impaired glucose metabolism can affect almost every tissue and organ system of the body [4]. Despite the tendency in patients with good metabolic control to have a significantly reduced risk of developing complications, vascular disease can continue to develop and progress even under intensive treatment regimens due to the phenomenon known as "glycemic memory" [5]. Increased glucose levels can lead to metabolic derangements associated with vision loss, peripheral neuropathy, myocardial infarction, strokes, foot ulcers, and end-stage renal disease, which may cause permanent disability [6].

4. **Kostov K**, Blazhev A. Serum Anti-Collagen IV IgM and IgG Antibodies as Indicators of Low Vascular Turnover of Collagen IV in Patients with Long-Term Complications of Type 2 Diabetes. Diagnostics. 2021; 11(5): 900. ISSN: 2075-4418, **Web of Science Q2 IF_{2021} 3.992, Scopus Q2 SJR_{2021} 0.658**

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Serum Anti-Collagen IV IgM and IgG Antibodies as Indicators of Low Vascular Turnover of Collagen IV in Patients with Long-Term Complications of Type 2 Diabetes

Krasimir Kostov [1,*] and Alexander Blazhev [2]

[1] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria
[2] Department of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; yalishanda9@gmail.com
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

Abstract: Thickening of the vascular basement membrane (BM) is a fundamental structural change in the small blood vessels in diabetes. Collagen type IV (CIV) is a major component of the BMs, and monitoring the turnover of this protein in type 2 diabetes (T2D) can provide important information about the mechanisms of vascular damage. The aim of the study was through the use of non-invasive biomarkers of CIV (autoantibodies, derivative peptides, and immune complexes) to investigate vascular turnover of CIV in patients with long-term complications of T2D. We measured serum levels of these biomarkers in 59 T2D patients with micro- and/or macrovascular complications and 20 healthy controls using an ELISA. Matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9) were also tested. In the T2D group, significantly lower levels of CIV markers and significantly higher levels of MMP-2 and MMP-9 were found compared to controls. A significant positive correlation was found between IgM antibody levels against CIV and MMP-2. These findings suggest that vascular metabolism of CIV is decreased in T2D with long-term complications and show that a positive linear relationship exists between MMP-2 levels and CIV turnover in the vascular wall.

Keywords: type 2 diabetes; collagen IV; vascular basement membrane; matrix metalloproteinases-2 and -9; diabetic vascular complications

Citation: Kostov, K.; Blazhev, A. Serum Anti-Collagen IV IgM and IgG Antibodies as Indicators of Low Vascular Turnover of Collagen IV in Patients with Long-Term Complications of Type 2 Diabetes. *Diagnostics* **2021**, *11*, 900. https://doi.org/10.3390/diagnostics11050900

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1. Introduction

Diabetes mellitus is a chronic disease with an increasing frequency in recent decade. The International Diabetes Federation (IDF) estimates that the global number of people with diabetes will increase to 693 million by 2045 [1]. Type 2 diabetes (T2D) accounts more than 90% of all diagnosed diabetes cases and is among the leading causes of cardiovascular morbidity and mortality [2]. In patients with T2D, the treatment of cardiovascular disease can be improved by identifying specific biomarkers to assess vascular changes [3].

Collagen (COL) is one of the primary load bearing components in the arterial wall and plays an important role in vascular function in both normal and pathological processes [4,5]. In patients with T2D, monitoring the turnover of this structural protein may provide important information about the mechanisms of vascular damage [6–12]. As a result of degradation processes occurring in the vascular extracellular matrix (ECM), the released COL peptides enter the circulation and can be detected and examined in the serum [13]. In this regard, the measurement of non-invasive markers of COL degradation, such as specific autoantibodies (autoAbs), COL-derived peptides (DP), and circulating immune complexes (CIC) of the COL, may be useful for monitoring the development of vascular complications in T2D [14–16].

Basement membranes (BMs) are a main focus of scientific research due to their role in the pathogenesis of a number of diseases [17]. Diabetes is a "BM disease", in which microvascular damage of the capillaries is characterized by thickening of the BMs [18–20]. COL type IV (CIV) is a major vascular BM protein and represents up to 50% of all BM

5. **Kostov K**, Blazhev A. Circulating Levels of Endothelin-1 and Big Endothelin-1 in Patients with Essential Hypertension. Pathophysiology. 2021; 28(4): 489-495. ISSN: 0928-4680, **Web of Science, Scopus Q2 SJR$_{2021}$ 0.431**

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Article

Circulating Levels of Endothelin-1 and Big Endothelin-1 in Patients with Essential Hypertension

Krasimir Kostov [1,*] and Alexander Blazhev [2]

[1] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria
[2] Department of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; yalishanda9@gmail.com
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

Abstract: The role of endothelin-1 (ET-1) in the pathogenesis of hypertension (HTN) is not clearly established. There is evidence that its circulating levels are elevated in some forms of experimental and human HTN, but this was not a consistent finding. Based on these controversial data, we tested serum levels of ET-1 and Big ET-1 (the precursor of ET-1) in patients with essential HTN, comparing the results with those of healthy normotensive controls. The levels of ET-1 and Big ET-1 were measured by ELISA. Our results in patients with essential HTN showed that the mean levels of ET-1 (5.01 ± 2.1 pg/mL) were significantly higher ($F = 6.34$, $p = 0.0144$) than the mean levels in the control group (3.2 ± 1.0 pg/mL). The levels of Big ET-1 in patients with essential HTN (0.377 ± 0.1 pmol/L) were similar to those in the control group (0.378 ± 0.07 pmol/L) and did not differ significantly ($F = 0.00$, $p = 0.9531$). These data suggest that ET-1, but not Big ET-1, may play an important role in the pathogenesis of primary HTN.

Keywords: essential hypertension; endothelin-1; big endothelin-1

Citation: Kostov, K.; Blazhev, A. Circulating Levels of Endothelin-1 and Big Endothelin-1 in Patients with Essential Hypertension. *Pathophysiology* **2021**, *28*, 489–495. https://doi.org/10.3390/pathophysiology28040031

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1. Introduction

Hypertension (HTN) is one of the most prevalent diseases worldwide and is among the most important risk factors for cardiovascular and cerebrovascular complications [1]. It is currently thought to be the result of disturbances in a number of neural, renal, hormonal, and vascular mechanisms regulating blood pressure (BP) [2], as crucial importance is given to the imbalance of a number of vasoactive substances [3]. In HTN, the delicate balance in the regulation of vascular tone is disturbed due to decreased bioavailability of NO and the overproduction of ET-1 [4,5].

ET-1 is a vasoactive peptide identified in 1988 by Yanagisawa and colleagues from the supernatant of porcine aortic endothelial cells (ECs). It is composed of 21 amino acids and two intrachain disulfide linkages in the molecule [6]. In the vasculature, ET-1 acts on ETA and ETB (ETB1 and ETB2) receptors located on the vascular smooth muscle cells (VSMCs) and ECs to induce vascular contraction or vasodilation [7]. Vasoconstrictive action of ET-1 is mainly mediated through ETA on VSMCs, while vasodilation is mediated through ETB1 on ECs [8].

The role of ET-1 in the pathogenesis of HTN is not clearly established. It is assumed that under physiological conditions, the vasodilating action of ET-1 may predominate, whereas under pathophysiological conditions, ET-1 may behave as a vasoconstrictor and play a role in the pathophysiology of HTN [9]. There is evidence that circulating levels of ET-1 are elevated in some forms of experimental and human HTN, but this was not a consistent finding in all forms of HTN [10]. Furthermore, some studies show that Big ET-1, the biological precursor of ET-1, may be a more accurate indicator of the degree of activation of the endothelin system compared to ET-1, as it has a longer half-life and slower clearance than ET-1 [11]. However, there are currently insufficient studies on Big ET-1 levels in patients with essential HTN. Based on these controversial data, we tested serum

6. **Kostov K**, Blazhev A. Elevated IgG and IgM Autoantibodies to Advanced Glycation End Products of Vascular Elastin in Hypertensive Patients with Type 2 Diabetes: Relevance to Disease Initiation and Progression. Pathophysiology. 2022; 29(3): 426-34. ISSN: 0928-4680, **Web of Science, Scopus Q2 SJR$_{2021}$ 0.431**

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Article

Elevated IgG and IgM Autoantibodies to Advanced Glycation End Products of Vascular Elastin in Hypertensive Patients with Type 2 Diabetes: Relevance to Disease Initiation and Progression

Krasimir Kostov [1,*] and Alexander Blazhev [2]

[1] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria
[2] Department of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; yalishanda9@gmail.com
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

Abstract: The increased glycation of elastin is an important factor in vascular changes in diabetes. Using the ELISA method, we determined serum levels of IgM and IgG autoantibodies to advanced glycation end products of vascular elastin (anti-AGE EL IgM and anti-AGE EL IgG) in 59 hypertensive patients with type 2 diabetes (T2D) and 20 healthy controls. Serum levels of matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9) and the C-reactive protein (CRP) were also determined. The levels of anti-AGE EL IgM antibodies in the T2D group were similar to those in the control group, while those of anti-AGE EL IgG antibodies were significantly higher ($p = 0.017$). Significant positive correlations were found between the levels of anti-AGE EL IgM antibodies and MMP-2 ($r = 0.322$; $p = 0.013$) and between the levels of anti-AGE EL IgG antibodies and CRP ($r = 0.265$; $p = 0.042$). Our study showed that elevated anti-AGE EL IgG antibody levels may be an indicator of the enhanced AGE-modification and inflammatory-mediated destruction of vascular elastin in hypertensive patients with T2D. Anti-AGE EL IgM antibodies may reflect changes in vascular MMP-2 activity, and their elevated levels may be a sign of early vascular damage.

Keywords: hypertension; type 2 diabetes; advanced glycation end products (AGEs); autoantibodies to AGEs of vascular elastin

Citation: Kostov, K.; Blazhev, A. Elevated IgG and IgM Autoantibodies to Advanced Glycation End Products of Vascular Elastin in Hypertensive Patients with Type 2 Diabetes: Relevance to Disease Initiation and Progression. *Pathophysiology* **2022**, *29*, 426–434. https://doi.org/10.3390/pathophysiology29030034

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1. Introduction

Diabetes mellitus is a chronic disease with an increasing frequency over the last decade [1], with type 2 diabetes (T2D) accounting for more than 90% of all diagnosed cases [2]. In the long term, patients with T2D are at increased risk of developing cardiovascular disease (CVD), and the identification of specific biomarkers may improve their treatment [3]. One group of biomarkers that can be used are the autoantibodies to advanced glycation end products (AGEs) [4,5].

AGEs are formed by non-enzymatic reactions between the carbonyl groups of reducing sugars, such as glucose, and the free amino groups of a number biomolecules in the body, via the Maillard reaction [6]. This reaction is followed by the generation of a reversible Schiff-base adduct, which rearranges into a more stable and covalently bonded Amadori product. The Amadori product then undergoes irreversible chemical modifications that generate AGEs [7]. The glycation process can affect all proteins in the body, including circulating, extracellular, and intracellular proteins, such as hemoglobin, albumin, insulin, immunoglobulins, low-density lipoproteins, lens crystalline proteins, collagen (COL), and elastin (EL) [8–10]. Other biomolecules, such as lipids and DNA, can also be modified in a similar way [11]. Particularly vulnerable to glycation are long-lived molecules such as COL and EL in the vascular extracellular matrix (ECM), due to the slow rate of their turnover [12,13]. In diabetes, AGEs can also be formed through the polyol pathway,

7. Blazhev A, Atanasova M, **Kostov K**, Doychinova T, Blazheva S, Karcheva M. Estimation of Ixodes ricinus (Acari: Ixodidae) Populations of Kaylaka Park in the Town of Pleven, Bulgaria. Insects. 2021; 12(9): 808. ISSN: 2075-4450, **Web of Science Q1 IF_{2021} 3.141, Scopus Q1 SJR_{2021} 0.71**

insects MDPI

Article

Estimation of *Ixodes ricinus* (Acari: Ixodidae) Populations of Kaylaka Park in the Town of Pleven, Bulgaria

Alexander Blazhev [1,*], Milena Atanasova [1], Krasimir Kostov [2], Tsetsa Doychinova [3], Svetla Blazheva [4] and Milena Karcheva [3]

[1] Department of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; milena.atanasova-radeva@mu-pleven.bg
[2] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; dr.krasi_kostov@abv.bg
[3] Department of Infectious Diseases and Epidemiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; doichinova_ceca@abv.bg (T.D.); milena_karcheva@abv.bg (M.K.)
[4] Department of Immunology, University Hospital, 5800 Pleven, Bulgaria; svetlabl@abv.bg
* Correspondence: yalishanda9@gmail.com; Tel.: +35-(99)-88986865

Simple Summary: Hard ticks transmit the etiological agents of numerous diseases. Kaylaka Park is a protected area, but part of it is designated for various outdoor activities. The aim of our study was to establish the presence of hard ticks in four urbanized areas and four areas that are not maintained and are natural wilderness areas (wild areas). The flagging method of collection was used. Temperature, relative humidity, both collection time and distance covered were measured during the sampling campaigns. The density of ticks collected was calculated, the number of ticks captured per minute was calculated and the results were compared between urban and wild areas over a five-year period (2016–2020). A total of 622 ticks were collected. All of them were identified as *Ixodes ricinus*. Significant differences between the urban and wild areas were observed in the number of ticks per minute and density of nymphs. The peak in questing tick activity has been established at the end of April. The highest yield was obtained at 20 °C and at 60% relative humidity. We found that the distribution of *Ixodes ricinus* ticks is widespread in Kaylaka Park. Their high density poses a serious risk to park visitors in both wild and maintained urban areas.

Abstract: (1) Background: Ticks are vectors of a large number of pathogenic microorganisms, which cause serious diseases in both humans and animals. Kaylaka Park is located in northern Bulgaria close to the city of Pleven. Part of the park is urbanized and visited daily by many citizens. The aim of our study was to determine the presence and distribution of hard ticks in the park area by surveying and comparing four urbanized with four wild areas. (2) Methods: Ticks were collected by flagging from 2016 to 2020 during the spring–summer season (March–July). Air temperature, relative humidity, collection time and flagging area were measured during the campaign. (3) Results: A total of 622 ticks were collected: 285 females (46%), 272 (44%) males and 64 (10%) nymphs. All were identified as *Ixodes ricinus*. Wild areas showed statistically significant higher values of ticks collected per minute ($p = 0.009$) and nymph densities ($p = 0.003$) compared to urbanized sampling sites. Other densities indices did not have a significant difference between urban and wild areas. Highest numbers of *Ixodes* ticks were collected at a temperature of 20 °C and at 60% relative humidity. The active questing began in March, peaked in end of April and declined in June. (4) Conclusions: In the present study, we found that ecological factors in the Kaylaka Park area are favourable for the development and distribution of tick populations. The results give us reason to consider that there is a high risk to visitors from tick bites in the Kaylaka Park area.

Keywords: *Ixodes ricinus*; tick collection; tick density; flagging; medical entomology; Kaylaka Park

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Citation: Blazhev, A.; Atanasova, M.; Kostov, K.; Doychinova, T.; Blazheva, S.; Karcheva, M. Estimation of *Ixodes ricinus* (Acari: Ixodidae) Populations of Kaylaka Park in the Town of Pleven, Bulgaria. *Insects* **2021**, *12*, 808. https://doi.org/10.3390/insects12090808

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8. Блажев А, Карчева М, Ценова А, Блажева С, **Костов К.** Серологични изследвания за лаймска борелиоза. Обща медицина. 2018; 3: 20-24. ISSN: 1311-1817, **НАЦИД, Scopus Q4 SJR_{2018} 0.101**

СЕРОЛОГИЧНИ ИЗСЛЕДВАНИЯ ЗА ЛАЙМСКА БОРЕЛИОЗА

А. Блажев[1], М. Карчева[2], А. Ценова[3], С. Блажева[4], К. Костов[5]

[1]Сектор „Биология", Медицински университет – Плевен

[2]Сектор „Епидемиология, паразитология и тропическа медицина", Медицински университет – Плевен

[3]Регионална здравна инспекция – Плевен

[4]Сектор „Клинична имунология и алергология", Медицински университет – Плевен

[5]Сектор „Патофизиология", Медицински университет – Плевен

SEROLOGICAL TESTS FOR LYME BORRELIOSIS

A. Blazhev[1], M. Karcheva[2], A. Tsenova[3], S. Blazheva[4], K. Kostov[5]

[1]Department of Biology, Medical University – Pleven

[2]Department of Epidemiology, Parasitology and Tropical medicine, Medical University – Pleven

[3]Regional Health Inspection – Pleven

[4]Department of Clinical Immunology and Allergology, Medical University – Pleven

[5]Department of Pathological Physiology, Medical University – Pleven

Резюме. *Лаймската борелиоза (ЛБ) е най-разпространената векторно преносима болест в Европа. Заразяването на хората с причинителя B. burgdorferi се реализира чрез ухапване от инфектиран кърлеж. Целта на настоящото проучване е да се оцени рискът от ЛБ в Плевен и региона въз основа на сероепидемиологични данни от регионалната здравна инспекция. Представени са данни от серологични изследвания за антиборелийни антитела за лаймска борелиоза, извършени в РЗИ – Плевен (2015-2017 г.). Приложени са следните серологични методи – ELISA IgM/IgG и имуноблот (Westernblot, WB IgM/IgG). Анамнестичните данни са набрани посредством анкетно проучване. За периода 2015-2017 г. в РЗИ – Плевен, са изследвани 181 серума от лица, претърпели ухапване от кърлеж. Месечното разпределение на постъпилите в лабораторията проби показва постепенно нарастване на броя им през летните месеци с пик през м. юли (n = 42). Половината (n = 85) от серумните проби, постъпили за изследване на ELISA IgM, са позитивни. Потвърдителен WB IgM тест е извършен на 76 проби, от които 10 (13.16%) са позитивни. Серопозитивни за ELISA IgG са 5/79 (6.33%) от изследваните проби. Надеждната лабораторна диагностика е от съществено значение за ранно откриване, наблюдение и контрол на заболяването.*

Ключови думи: *лаймска борелиоза, серологични тестове, ELISA IgM/IgG, WB IgM/IgG*

Abstract. *Lyme borreliosis (LB) is one of the most prevalent vector-borne diseases in Europe. The infection of humans with the B. burgdorferi agent is accomplished by biting from an infected tick. The purpose of this study was to assess the risk of LB in Pleven and the region based on sero-epidemiological data from the Regional Health Inspection. Data from serological tests for anti-borrelia antibodies were presented from the Regional Health Inspection-Pleven. The following serological methods - ELISA IgM/IgG and Immunoblot (Western blot, WB IgM/IgG) are applied. Anamnestic data were collected through a questionnaire. For the period 2015-2017, 181 sera of subjects with a tick bite were examined in Regional Health Inspection – Pleven. The monthly distribution of the samples received in the laboratory shows a gradual increase in their number in the summer months with a peak in July (n = 42). Half (n = 85) of the serum samples received for ELISA IgM testing were positive. A confirmatory WB IgM test was performed on 76 samples, of which 10 (13.16%) were positive. Seropositive for ELISA IgG were 5/79 (6.33%) of the tested samples. Interpretation of serological assays in context of clinical symptom is important for early detection, monitoring and control of the disease.*

Key words: *Lyme borreliosis, serological tests, ELISA IgM/IgG, WB IgM/IgG*

9. Grigoryan A, Dimitrova A, **Kostov K**, Ruseva A, Atanasova M, Blazhev A, Betova T. Serum concentrations of metalloproteinases -9, -13 and TIMP-1 in an ovariectomized wistar rat model of osteoporosis. Archives of the Balkan Medical Union. 2017; 52(4): 391-396. ISSN: 1584-9244, **Scopus Q3 SJR$_{2017}$ 0.192**

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ORIGINAL STUDY

SERUM CONCENTRATIONS OF MATRIX METALLOPROTEINASE-9, -13 AND TIMP-1 IN AN OVARIECTOMIZED WISTAR RAT MODEL OF OSTEOPOROSIS

Armine V. Grigoryan[1], Anelia A. Dimitrova[1], Krasimir G. Kostov[1], Adelaida L. Ruseva[2], Milena A. Atanasova[3], Alexander B. Blazhev[3], Tatyana M. Betova[4]

[1] Department of Physiology and Pathophysiology, Medical University - Pleven, Bulgaria
[2] Department of Clinical Laboratory, Medical University - Pleven, Bulgaria
[3] Department of Biology, Medical University - Pleven, Bulgaria
[4] Department of Pathoanatomy, Medical University - Pleven, Bulgaria

Abstract

Introduction. Osteoporosis is a disease characterized by decreased bone density and destruction of the microarchitectonics of the bone structure. This leads to increased bone fragility and risk of fracture particularly of the hip, spine, wrist and shoulder. Osteoporosis is known as „The Silent Epidemic of the Century" because bone loss occurs without symptoms. Altered ovarian function is one of the most common causes of osteoporosis. Indicators for altered bone homeostasis are the changes in serum levels of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs).
Objective. The aim of current study was to determine the activity of alkaline phosphatase (ALP) and serum concentrations of MMP-9, MMP-13 and TIMP-1 in the ovariectomized rats.
Materials and Methods. An experiment was performed on 35 female Wistar rats at reproductive age - 2 months divided into 2 groups: group 1 (G1)-20 animals were sham-operated (sham) and group 2 (G2)-15 were ovariectomized (ovx).

Résumé

Concentrations du sérum des métallo-protéinases matricielles-9, -13 et TIMP-1 dans un modèle d'ostéoporose à déficit ostrogénique d'un rat Wistar femelle

Introduction. L'ostéoporose est une maladie caractérisée par une diminution de la densité de la masse osseuse et la destruction de la micro-architecture de la structure osseuse. Cela conduit à une fragilité osseuse accrue et à un risque de fracture, en particulier de la hanche, de la colonne vertébrale, du poignet et de l'épaule. L'ostéoporose est connue comme «l'épidémie silencieuse du siècle» parce que la perte osseuse se produit sans symptômes.L'altération de la fonction ovarienne est l'une des causes les plus fréquentes de l'ostéoporose. Les indicateurs de l'altération de l'homéostasie osseuse sont les changements dans les taux sériques des métallo-protéinases matricielles (MMPs) et de leurs inhibiteurs tissulaires (TIMPs).
Objectifs. Le but de cette étude était de déterminer l'activité de la phosphatase alcaline (ALP) et

Corresponding author: Armine Grigoryan
Department of „Physiology and Pathophysiology", Medical University-Pleven
„Kliment Ohridski" Str., N° 1, 5800 Pleven, Bulgaria
e-mail: armine14@abv.bg; phone: 0886-31-99-33

10. Grigoryan A, Dimitrova A, **Kostov K**, Ruseva A, Atanasova M, Blazhev A, Betova T, Trifonov R. Changes of serum concentrations of alkaline phosphatase and metalloproteinase-9 in an ovarectomized wistar rat model of osteoporosis. Journal of Biomedical and Clinical Research. 2017; 10(1): 32-35. ISSN: 1313-6917, **НАЦИД, (Web of Science 2014-) (CABI)**

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Original Articles

CHANGES OF SERUM CONCENTRATIONS OF ALKALINE PHOSPHATASE AND METALLOPROTEINASE-9 IN AN OVARIECTOMIZED WISTAR RAT MODEL OF OSTEOPOROSIS

Armine V. Grigoryan,
Aneliya A. Dimitrova,
Krasimir G. Kostov,
Adelaida L. Russeva[1],
Milena A. Atanasova[2],
Alexander B. Blagev[2],
Tatyana M. Betova[3],
Radoslav G. Trifonov[4]

Department of Pathological Physiology,
Medical University – Pleven,
Bulgaria
[1]Department of Clinical Laboratory,
Medical University – Pleven,
Bulgaria
[2]Department of Biology,
Medical University – Pleven,
Bulgaria
[3]Department of Patholoanatomy,
Medical University – Pleven,
Bulgaria
[4]Student of Medical University – Pleven,
Bulgaria

Corresponding Author:
Armine V. Grigoryan
Department of Pathological Physiology,
Medical University – Pleven
1, St. Kliment Ohridski Str.
Pleven, 5800
Bulgaria
e-mail: armine14@abv.bg

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Summary

Osteoporosis is a systemic skeletal disease characterized by decreased bone mass, destruction of the microarchitectonics of bone structure and a high risk for fracture. One of the criteria for altered bone homeostasis includes the changes in serum levels of alkaline phosphatase (ALP) and the activity of matrix metalloproteinases (MMPs). The purpose of this study was to determine the serum concentrations of calcium (Ca^{2+}), phosphorus (P), magnesium (Mg^{2+}), alkaline phosphatase (ALP) and MMP-9 in ovariectomized rats. We used 35 female Wistar rats at reproductive age (2 months) divided into 2 groups: a control group (G1-SHAM) – 20 animals subjected to "false" ovariectomy and placebo-operation, and an ovariectomized group (G2-OVX) – 15 animals subjected to bilateral ovariectomy. Blood was collected from the abdominal aorta for testing levels of Ca^{2+}, P, Mg^{2+}, ALP and MMP-9. No statistically significant differences in serum concentrations of Ca^{2+}, P and Mg^{2+} were found between G2 and G1 ($p>0.05$). The values of ALP and MMP-9 in rats of G2 were statistically significantly increased, as compared to G1 ($p<0.05$). The serum activity of ALP, which is a marker for bone formation, was increased in OVX-induced osteoporosis. Elevated serum MMP-9 levels in G2 confirmed the hypothesis that it is a marker for osteoclast activity.

Key words: osteoporosis, MMP-9, ALP

Introduction

According to the WHO, osteoporosis is a progressive systemic disease of the bone tissue, characterized by decreased mass and deteriorated microartictonics of the bone, leading to increased bone fragility and risk of fractures [1].

There is a variety of causes of osteoporosis. It is estimated that 10% of the human skeleton is annually updated due to the controlled and regulated activity of osteoclasts (Oc) and osteoblasts (Ob) [2]. The pathological processes that disrupt the balance between the activity of these two cell groups lead to increased bone fragility and brittleness. During menopause or after ovariectomy the level of estrogens falls and this hormone deficiency contributes to the destruction of the bones by activating osteoclasts [3, 4] and increased expression of matrix metalloproteinases (MMPs) [5,

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Review

Effects of Magnesium Deficiency on Mechanisms of Insulin Resistance in Type 2 Diabetes: Focusing on the Processes of Insulin Secretion and Signaling

Krasimir Kostov

Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

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Abstract: Magnesium (Mg^{2+}) is an essential mineral for human health and plays an important role in the regulation of glucose homeostasis and insulin actions. Despite the widespread clinical evidences for the association of Mg^{2+} deficiency (MgD) and type 2 diabetes mellitus (T2D), molecular mechanisms by which Mg^{2+} contributes to insulin resistance (IR) are still under discussion. Mg^{2+} regulates electrical activity and insulin secretion in pancreatic beta-cells. Intracellular Mg^{2+} concentrations are critical for the phosphorylation of the insulin receptor and other downstream signal kinases of the target cells. Low Mg^{2+} levels result in a defective tyrosine kinase activity, post-receptor impairment in insulin action, altered cellular glucose transport, and decreased cellular glucose utilization, which promotes peripheral IR in T2D. MgD triggers chronic systemic inflammation that also potentiates IR. People with T2D may end up in a vicious circle in which MgD increases IR and IR causes MgD, that requires periodic monitoring of serum Mg^{2+} levels.

Keywords: magnesium deficiency; insulin resistance; type 2 diabetes; insulin secretion; insulin signaling

1. Introduction

Insulin resistance (IR) is associated with an impaired biological response to insulin stimulation of key target tissues, particularly liver, muscle, and adipose tissue. IR impacts glucose utilization, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia [1]. Progression of IR can lead to metabolic syndrome (MetS) and type 2 diabetes mellitus (T2D) [2]. According to the International Diabetes Federation, one in every 11 adults has diabetes and T2D accounts for more than 90% of these cases [3]. Globally, 500 million adults are expected to have T2D by 2030 [4].

Magnesium (Mg^{2+}) is the fourth most common mineral in the human body, after calcium (Ca^{2+}), potassium (K^{+}), and sodium (Na+), and the second most abundant intracellular cation after K^{+} [5]. Currently, enzymatic databases list over 600 enzymes for which Mg^{2+} serves as cofactor and an additional 200 in which Mg^{2+} may act as activator [6]. Only 1% of the total Mg^{2+} in the body is present in extracellular fluids and only 0.3% is found in the serum [5]. The normal reference range for Mg^{2+} in the serum is 0.76–1.15 mmol/L. Magnesium deficiency (MgD) is a condition where the serum concentration of Mg^{2+} in the body is $\leq$0.75 mmol/L (1.8 mg/dL) [6]. Mg^{2+} concentrations $\leq$0.75 mmol/L may be considered as preclinical hypomagnesemia. Patients are considered frankly hypomagnesemic with serum Mg^{2+} concentrations $\leq$0.61 mmol/L (1.5 mg/dL). MgD can be present without hypomagnesemia. However, hypomagnesemia, when present, is usually indicative of an important systemic Mg^{2+} deficit [7]. Signs and symptoms of hypomagnesemia usually occur when serum Mg^{2+} is decreased below 0.5 mmol/L (1.2 mg/dL) [7]. A number of factors can negatively

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life

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Review

The Causal Relationship between Endothelin-1 and Hypertension: Focusing on Endothelial Dysfunction, Arterial Stiffness, Vascular Remodeling, and Blood Pressure Regulation

Krasimir Kostov

Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

Abstract: Hypertension (HTN) is one of the most prevalent diseases worldwide and is among the most important risk factors for cardiovascular and cerebrovascular complications. It is currently thought to be the result of disturbances in a number of neural, renal, hormonal, and vascular mechanisms regulating blood pressure (BP), so crucial importance is given to the imbalance of a number of vasoactive factors produced by the endothelium. Decreased nitric oxide production and increased production of endothelin-1 (ET-1) in the vascular wall may promote oxidative stress and low-grade inflammation, with the development of endothelial dysfunction (ED) and increased vasoconstrictor activity. Increased ET-1 production can contribute to arterial aging and the development of atherosclerotic changes, which are associated with increased arterial stiffness and manifestation of isolated systolic HTN. In addition, ET-1 is involved in the complex regulation of BP through synergistic interactions with angiotensin II, regulates the production of catecholamines and sympathetic activity, affects renal hemodynamics and water–salt balance, and regulates baroreceptor activity and myocardial contractility. This review focuses on the relationship between ET-1 and HTN and in particular on the key role of ET-1 in the pathogenesis of ED, arterial structural changes, and impaired vascular regulation of BP. The information presented includes basic concepts on the role of ET-1 in the pathogenesis of HTN without going into detailed analyses, which allows it to be used by a wide range of specialists. Also, the main pathological processes and mechanisms are richly illustrated for better understanding.

Keywords: endothelin-1; hypertension; oxidative stress; low-grade inflammation; endothelial dysfunction; arterial stiffness; arterial remodeling; blood pressure regulation

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1. Introduction

Hypertension (HTN) is one of the most prevalent socially significant diseases and is among the most important preventable risk factors for other diseases [1]. The heart, brain, kidneys, and peripheral arteries are often affected, which is a cause of early disability and reduced life expectancy in patients [2]. This necessitates that the prevention and treatment of HTN be among the top priorities of public health worldwide [3].

HTN is a heterogeneous disease with a complex pathogenesis. It is currently thought to be the result of disturbances in a number of neural, renal, hormonal, and vascular mechanisms regulating blood pressure (BP) [4], as crucial importance is given to the imbalance of a number of vasoactive substances, some of which are produced from the vascular endothelium [5]. The endothelium responds to humoral, neural, and especially hemodynamic stimuli, and regulates platelet function, inflammatory responses, growth and migration of vascular smooth muscle cells (VSMCs), and changes in the structure of the vascular extracellular matrix [6,7]. In addition to these functions, it modulates vascular tone by synthesizing and releasing a number of vasoactive factors that may have vasodilatory effects, such as nitric oxide (NO), prostacyclin (PGI_2), and endothelium-derived hyperpolarizing factor, and vasoconstrictor effects, such as thromboxane A_2 and endothelin-1 (ET-1) [8]. In

13. Kostov K, Dimitrova A, Tisheva S, Ruseva A, Blazhev A, Atanasova M, Gospodinov K. C-reactive protein as a marker for low-grade inflammation in hypertensive patients with and without type 2 diabetes mellitus. "Science and Youth" 2015, Plovdiv, 106-109. ISSN: 1314-9229

C-reactive Protein as a Marker for Low-grade Inflammation in Hypertensive Patients with and without Type 2 Diabetes Mellitus

Krasimir Kostov[1], Anelia Dimitrova[1], Snejana Tisheva[2], Adelaida Ruseva[3], Milena Atanasova[4], Aleksander Blazhev[4], Konstantin Gospodinov[2]

[1]Department of Pathophysiology, Medical University – Pleven, Bulgaria
[2]Department of Cardiology and Rheumatology, Medical University – Pleven, Bulgaria
[3]Central Clinical Laboratory of University Hospital, Pleven, Bulgaria
[4]Department of Biology, Medical University – Pleven, Bulgaria

e-mail: dr.krasi_kostov@abv.bg

Introduction

Inflammation is recognized as a central mechanism contributing to progression of cardiovascular diseases (1). Recently, chronic low-grade inflammation has been identified as an integral part in the pathogenesis of vascular disease. Prospective clinical studies have shown that systemic chronic low-grade inflammation is associated with an increased risk of cardiovascular events and mortality (2). Low-grade inflammation localized in vascular tissue is recognized as an important contributor to the pathophysiology of hypertension (3).

C-reactive protein (CRP), among other systemic inflammatory mediators, has been widely accepted as a potent risk indicator, independently predicting future cardiovascular events. The impact of CRP on cardiovascular outcome has been corroborated by a large number of observational studies and meta-analyses. These studies show, that an elevated CRP has a clear prognostic value for major cardiovascular events and mortality, whereas the lowering of CRP is associated with a reduction in cardiovascular risk (4,5). For example, plasma CRP levels are a powerful predictor of ischemic cardiovascular events (stroke, peripheral vascular disease, sudden cardiac death and myocardial infarction) in patients with stable or unstable angina, and even among apparently healthy subjects. Elevated CRP levels appear to correlate with softer plaques that are more prone to rupture (1). Combining these findings with experimental observations has lead to a paradigm shift in which CRP is no longer merely a marker, but is increasingly considered as a mediator of cardiovascular disease (4). CRP is a 115-kDa pentamer expressed almost exclusively by hepatocytes as part of the non-specific acute-phase response to tissue damage, infection and inflammation (1). The main inducer of the response, however, is another important pro-inflammatory cytokine, interleukin 6 (IL-6). Interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α), also stimulate CRP releasing (6).

The idea that hypertension and inflammation are somehow linked emerges from the recent crosssectional and prospective studies, showing that circulating inflammatory molecules are increased in hypertensive patients, and their levels predict the onset of hypertension (7). There is evidence in both human and

14. Kostov K. Endothelin-1 and Hypertension. Encyclopedia MDPI. 2021; 1-6. ISSN: 2309-3366

Endothelin-1 and Hypertension

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Submitted by: Krasimir Kostov
(This entry belongs to Entry Collection "Hypertension and Cardiovascular Diseases")

Definition

Hypertension (HTN) is one of the most prevalent diseases worldwide and is among the most important risk factors for cardiovascular and cerebrovascular complications. It is currently thought to be the result of disturbances in a number of neural, renal, hormonal, and vascular mechanisms regulating blood pressure (BP), so crucial importance is given to the imbalance of a number of vasoactive factors produced by the endothelium.

1. Introduction

Hypertension (HTN) is one of the most prevalent socially significant diseases and is among the most important preventable risk factors for other diseases [1]. The heart, brain, kidneys, and peripheral arteries are often affected, which is a cause of early disability and reduced life expectancy in patients [2]. This necessitates that the prevention and treatment of HTN be among the top priorities of public health worldwide [3].

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ET-1 was first isolated in 1988 by Yanagisawa and colleagues from the culture supernatant of porcine aortic endothelial cells (ECs). It is composed of 21 amino acids and two intrachain disulfide linkages in the molecule [11]. Shortly after the discovery of ET-1, two other structurally similar isopeptides, named ET-2 and ET-3, were isolated [12]. ET-1 is the predominant isopeptide involved in regulating the cardiovascular system, and vascular ECs are the most abundant source of ET-1. In addition to ECs, ET-1 is expressed in a wide variety of cells including VSMCs, cardiomyocytes, fibroblasts, macrophages, epithelial cells in the lungs and kidneys, neurons, and glial cells [13]. The endothelins (ETs) are produced from their corresponding approximately 200-residue prepropolypeptides that are encoded by three distinct genes. These peptides are converted into inactive 38- or 39-amino acid intermediates called Big ETs (Big ET-1, Big ET-2, and Big ET-3) by furin-like endopeptidase. The Big ETs are then activated via proteolytic cleavage by the ET-converting enzymes (ECEs), ECE-1 and ECE-2 [14] (**Figure 1**).

15. Костов К, Димитрова А, Григорян А, Тишева С, Русева А, Атанасова М, Господинов К, Блажев А. Промени в серумните концентрации на ендотелин-1 и С-реактивния протеин при пациенти с лека и тежка степен на артериална хипертензия. Сборник доклади и резюмета от XII Национална научна сесия за студенти и преподаватели, МУ-Плевен, 2014, 264-268. ISBN: 978-954-756-150-2

ПРОМЕНИ В СЕРУМНИТЕ КОНЦЕНТРАЦИИ НА ЕНДОТЕЛИН-1 (ЕТ-1) И С- РЕАКТИВНИЯ ПРОТЕИН ПРИ ПАЦИЕНТИ С ЛЕКА И ТЕЖКА СТЕПЕН НА АРТЕРИАЛНА ХИПЕРТЕНЗИЯ

К. Костов[1], А. Димитрова[1], А. Григорян[1], С. Тишева[2], А. Русева[3], М. Атанасова[4], К. Господинов[2], А. Блажев[4]

[1]Катедра „Физиология и патофизиология"
[2]Катедра „Кардиология, пулмология и ендокринология"
[3]Катедра „Клинична лаборатория, клинична имунология и алерголгия"
[4]Катедра „Анатомия, хистология, цитология и биология", Сектор „Биология" Сектор „Патофизиология"
Катедра „Физиология и патофизиология", МУ-Плевен

Резюме

Въведение: Хемодинамичният стрес при артериална хипертензия води до повишена продукция на ендотелин-1, който е един от най-силните открити до момента вазоконстриктори. С-реактивният протеин е острофазов белтък, който се синтезира от хепатоцитите под въздействието на интерлевкин-6 (IL-6), интерлевкин-1b (IL-1b) и тумор некротизиращ фактор-а (TNF-a) при възпаление.

Цел: Настоящото изследване има за цел да проучи връзката на ЕТ-1 и CRP със степента на артериалната хипертензия и възпалителния системен и съдов отговор.

Методи: Сформирани бяха три групи: I група- 31 пациента с лека хипертензия- ЛХ (АН е"140/90 и d"160/100); II група- 29 пациента с тежка хипертензия- ТХ (АН е"160/100); III група-15 лица, контролна група- КГ (АН е"120/80 и d"130/85). ЕТ-1 е определен чрез ELISA kit на „Biomedika", а CRP- чрез имунотурбидиметричен метод с латексови частици покрити с моноклонални анти-CRP антитела. За анализите е използвана статистическа програма STATGRAPHICS.

Резултати и обсъждане: Експерименталните данни от изследването показват, че серумните нива на ЕТ-1 са повишени при артериалната хипертензия ($p<0,05$), което доказва ролята му в патогенезата на заболяването. Стойностите на ЕТ-1 в групата с ЛХ са по-високи от тези при ТХ, което показва, че ЕТ-1 играе основна роля за хипертензивното състояние още в началните етапи, преди да са настъпили процесите на стабилно съдово ремоделиране. Средните концентрации на CRP при ЛХ и ТХ са значително повишени, което потвърждава патогенетичната връзката на артериалната хипертензия със системното и съдово възпаление. Те са по-високи при пациентите с ЛХ в сравнение с КГ ($p<0,05$) и тези с ТХ, което показва, че възпалителният процес е доминиращ в ранните стадии на хипертоничната болест.

Ключови думи: артериална хипертензия, ендотелин-1, С-реактивен протеин

Въведение. Хипертонията е многофакторно заболяване, което е свързано с патологични промени в нервните, бъбречните, хормоналните и съдовите механизми за контрол на кръвното налягане. Най-важната регулация се осъществява на нивото

16. Григорян А, **Костов К**, А. Димитрова. Влияние на MMPs върху съдовата стена. Сборник с научни съобщения от конкурсна сесия „Наука и младост" 2012, МУ-Пловдив, 232-239. ISSN: 1314-9229

ВЛИЯНИЕ НА MMPS ВЪРХУ СЪДОВАТА СТЕНА

Армине Григорян, Красимир Костов, Анелия Димитрова
Катедра „Физиология и патофизиология", Факултет по медицина, Медицински университет - Плевен

Матриксните металопротеинази (MMPs) са увеличаваща се фамилия от Zn- и Ca-съдържащи ендопептидази със сходни функционални домейни и механизъм на действие свързан с разграждане компонентите на екстрацелуларния матрикс (ЕЦМ).

Свръхекспресията и повишената активност на MMPs, както и дисбаланса между MMPs и тъканните им инхибитори (TIMPs) се наблюдава при много физиологични и патологични промени, като органно развитие, зарастване на рани, възпаление, онкологични заболявания и атеросклероза (1).

Понастоящем са известни около 28 различни вида MMPs, класифицирани в групи според вида на протеолитичния субстрат, който те разграждат. Семейството на MMPs включва: колагенази (MMP-1,-8 и -13), желатинази (MMP-2 и -9), стромелизини (MMP-3,-10,-11), матрилизини (MMP-7 и -26), тип-мембранни MMPs (MMP-14,-15,-16,-17 и MMP-23,-24,-25), енамелизини (MMP-20), металоеластази (MMP-12) и други MMPs (MMP-19,-21,-27,-28) (2).

Всички MMPs имат сходна структура: про-пептид, каталитичен домейн и haemopexin като С-терминален домейн, който от своя страна е свързан с каталитичния домейн чрез гъвкава връзка. MMPs се секретират в латентни проформи, изискващи активация за превръщането им в активни ензими (3).

Регулацията на MMPs е изключително важна в здравата тъкан, тъй като след активирането им, могат напълно да разградят всички екстрацелуларни компоненти. Поради тази причина, дейността на тези ензими се намира под строг контрол, който се осъществява на три нива: транскрипция, активация и секреция на латентни проензими, и протеолитично инхибиране.

Транскрипция

Инициращи стимули за транскрипция се явяват различни цитокини и растежни фактори като: IL-1, PDGF (тромбоцитен растежен фактор) и TNF-α, докато други, като напр.TGF-ß (трансформиращ растежен фактор-ß), хепарин и кортикостероиди имат инхибиторен ефект. Много от тези цитокини и растежни фактори са важни медиатори,

17. Григорян А, **Костов К**, Димитрова А, Бетова Т, Апостолова М. Имунохистохимично изследване на експресията на ендотелин-1 в абдоминалната аорта при пациенти с атеросклероза. Сборник с научни съобщения от конкурсна сесия „Наука и младост" 2013, МУ-Пловдив, 41-45. ISSN: 1314-9229

Имунохистохимично изследване на експресията на ендотелин-1 в абдоминалната аорта при пациенти с атеросклероза

Армине Григорян[1], Красимир Костов[1], Анелия Димитрова[1], Татяна Бетова[2], Маргарита Апостолова[3]

[1]Катедра „Физиология и патофизиология" – МУ Плевен
[2]Катедра „Обща и клинична патология" – МУ Плевен
[3]Институт по молекулярна биология, Лаборатория по медико-биологични изследвания БАН – София
Сектор „Патофизиология"
Катедра „Физиология и патофизиология" – МУ Плевен

e-mail: armine14@abv.bg

Въведение

Атеросклерозата е мултифакторно заболяване засягащо големите и средни по размер артерии, което се изразява в локално отлагане на липиди в артериалната стена и формиране на плаки, прояви на исхемия и/или тъканна некроза в областта на засегнатите участъци (1). Най-различни етиологични фактори въздействат и увреждат интимата на съда, което става предпоставка за развитието на атеросклерозата. Съществена роля за атерогенезата се отдава на дислипидемията (2) и ендотелната дисфункция (3), като от значение е и оксидативния стрес на съдовата стена (4) и възпалението (5).

Ендотелин-1 (ET-1) е съдов пептид с мощно вазоконстрикторно действие, който се продуцира основно от ендотелните, но също така и от гладкомускулните клетки (ГМК) на съдовата стена. Той се образува от неактивен предшественик означен като Big-ET-1. Благодарение на специфична ендопептидаза препро-ET-1 се превръща Big-ET-1, а чрез ендотелин-конвертиращия ензим-1 (ECE-1), неактивния Big-ET-1 се превръща в ET-1 (6). Основни активатори за синтеза на ET-1 в организма се явяват хипоксията, хемодинамичния съдов стрес, ангиотензин II, катехоламини, тромбин, тромбоксан A_2, окислените липопротеини (Ox-LDL) и др. фактори (7). Всички те водят до ендотелна дисфункция и възпалителен отговор на съдовата стена, които се явяват основни причини за секрецията на ET-1 (3).

Цел и задачи

Целта на нашето изследване е да се определи степента на имунохистохимичната експресия на ET-1 в абдоминалната аорта при пациенти с и без атеросклероза и да се сравни експресията на ET-1 при различните етапи на атеросклеротичното развитие.

Материали и методи

За едногодишен период са изследвани сегменти от 26 броя човешки абдоминални аорти на пациенти с различни заболявания взети при аутопсия до петия час след смъртта в Катедра „Обща и клинична патология" – Медицински университет, Плевен. Приложени са рутинни хистологични методи (хематокси-

18. Григорян А, **Костов К**, Дишева В, Димитрова А. Участие на матриксните металопротеинази в патогенезата на остеопорозата. Сборник с научни съобщения от конкурсна сесия „Наука и младост" 2014, МУ-Пловдив, 51-56. ISSN: 1314-9229

Участие на матриксните металопротеинази в патогенезата на остеопорозата

А. Григорян[1], К. Костов[1], В. Дишева[2], А. Димитрова[1]

[1]Катедра „Физиология и патофизиология", Факултет по медицина, Медицински университет – Плевен
[2]Студент 4 курс, Факултет по медицина, Медицински университет – Плевен

e-mail: д-р Армине Григорян – armine14@abv.bg

Остеопорозата е многофакторно заболяване, което засяга скелета и се характеризира с намаляване на костната маса, разрушаване на микроархитектониката на костната структура и повишен риск от фрактури (1). По данни на Световната здравна организация, около 70 милиона души по света имат остеопороза (1). Подобни данни за Европа сочат, че до 2040 година броят на пациентите ще се удвои (2). Едно от най-тежките усложнения на заболяването са фрактурите на бедрената кост и гръбначния стълб (3). Остеопорозата се нарежда на трето място сред неинфекциозните заболявания, след сърдечно-съдови заболявания и онкологични проблеми (4). Особено сериозен е проблемът в България. У нас всяка година се регистрират над 90 хил. счупвания в резултат на остеопороза.

Основните хормони, които регулират костния метаболизъм са: паратхормон, калцитонин, витамин D_3, стероидни хормони, като естроген и тестостерон, растежен хормон, тироксин, кортизол, инсулин, инсулиноподобния растежен фактор (IGF-I) и др. Вродената липса или придобитият дефицит на всеки един от тези хормони може да доведе до загубата на костна структура, водеща до развитието на остеопороза (5).

Ключът към разбирането на патогенезата на остеопорозата е анализът на процеса на костно ремоделиране. Във връзка с това са натрупани достатъчно данни за развитието на процесите на клетъчно и молекулярно ниво, но все още липсва цялостна информация за факторите, които регулират костно ремоделиране при хора (6).

Костната резорбция и формирането на коста са два взаимно балансиращи се процеса при здрави хора. Резорбцията от остеокластите е последвана от активиране на остеобластите и образуване на остеоид, който запълва кухините за период от около три месеца. Когато синтезът на матрицата е завършен, остеобластите се вграждат в нея и започват да функционират като остеоцити. Последните продължават да играят основна роля в инициирането на костното ремоделиране чрез предаване на сигнали към остеобластите и остеокластите върху костната повърхност (7). След 30-годишна възраст костната маса намалява, а след менопаузата загубата достига до 15%. В началото тя се дължи на повишена костна резорбция, а по-късно на потисната остеобластна активност. Като цяло естрогенният дефицит е един от основните фактори за развитието на остеопорозата (8), включително и при млади жени след овариектомия (9).

Последни проучвания показват, че в процесите на костното ремоделиране

19. Григорян А, Димитрова А, **Костов К**. Остеопороза и хранителен режим. Сборник с публикации от X-ти Национален конгрес по хранене с международно участие. Науката за хранене с авторитетно настояще и престижно бъдеще. София, 2016: 126-128. ISBN: 978-954-9977-68-4

ОСТЕОПОРОЗА И ХРАНИТЕЛЕН РЕЖИМ

А. Григорян, А. Димитрова, К. Костов
Катедра „Физиология и патофизиология", Медицински университет – Плевен

OSTEOPOROSIS AND NUTRITION

A. Grigoryan, A. Dimitrova, K. Kostov
Department of „Physiology and Pathophysiology", Medical University – Pleven

Резюме: Остеопорозата е прогресиращо метаболитно заболяване на скелета, което се характеризира с намаляване на костната маса, разрушаване на микроархитектониката на костната структура и повишен риск от фрактури. Заболяването е широко разпространено сред възрастното население, особено при жени в менопауза, но има и много случаи на по-ранни форми на остеопороза. Удължаването на средната продължителност на живота и застаряването на населението увеличава значимостта на това заболяването и броя на пострадали от остеопороза. Болестта заема трето място сред сърдечно-съдовите и онкологични заболявания. В началните етапи протичането на болестта е безсимптомно и поради тази причина остеопорозата е наречена „тихата епидемия на века". Причините за развитието на остеопорозата са различни. Една от тях е неправилното хранене, което е корегируем рисков фактор в развитието на остеопорозата. Небалансираното и нездравословно хранене в детска и юношеска възраст е предпоставка за развитието на болестта в по-напреднал етап от живота. Включването в дневния порцион на фитоестрогени (съдържащи се в соята, редица зеленчуци, зърнени и бобови храни), калций съдържащи продукти и храни, богати на микроелементи и витамини (цинк, манган, магнезий, витамин D) при жени с естрогенен дефицит би намалило или отложило изявата на заболяването.

Abstract: Osteoporosis is a progressive metabolic disease of the skeleton that is characterized by loss of bone mass, destruction of bone micro-architecture and increased risk of fracture. The disease is a widespread among the adult population, especially in postmenopausal women, but there are many cases of earlier forms of osteoporosis. The extension of the average life expectancy and an aging population are increasing the importance of this disease and the number of affected by osteoporosis. Disease ranks third among cardiovascular and oncological diseases. In the initial stages course of the disease is asymptomatic and because of this reason osteoporosis is called "the silent epidemic of the century." The causes of the development of osteoporosis are different. One of them is malnutrition, which is a changeable risk factor in the development of osteoporosis. The unbalanced and unhealthy diets in childhood and adolescence is a prerequisite for the development of the disease in an advanced stage of life. Inclusion in the daily ration of phytoestrogens (contained in soybeans, some vegetables, grains and legumes), calcium-containing products and foods rich in vitamins and microelements (zinc, manganese, magnesium, vitamin D) in women with estrogen deficiency would reduce or postpone the manifestation of the disease.

Остеопорозата е прогресиращо метаболитно заболяване на скелета, което се характеризира с намаляване на костната маса, разрушаване на микроархитектониката на костната структура и води до повишен риск от фрактури (17).

В костната тъкан се извършва непрекъснат процес на ремоделиране при различни физиологични и патологични състояния. Нарушената регулацията на този процес води до развитието на остеопороза. Заболяването намалява силата на костите и едновременно с това те губят минералното си съдържание, което променя скелетната структура. В резултат на това костите стават лесно чупливи, гръбначният стълб се превива и се нарушава правилната стойка (21).

Съществуват три основни нефармакологични начини за превенция на остеопорозата: физически упражнения, подходящ хранителен режим и прием на хранителни добавки. Най-разумният подход е тези методи да се съчетават (1). При нужда може да се приложи и фармакологично лечение.

Много важно е редовното провеждане на опре-

20. Halacheva L, Kolev N, **Kostov K**. Basics of magnesium homeostasis, Science & Technologies, Volume V, Number 1, 2015, Medicine, 33-37. ISSN: 1314-4111

BASICS OF MAGNESIUM HOMEOSTASIS

Lyudmila Halacheva, Nikolai Kolev, Krasimir Kostov
Department of „Physiology and Pathophysiology"
Medical University-Pleven, 1„Kliment Ohridski" Str.,5800 Pleven, Bulgaria
E-mail:l_halacheva@abv.bg

ABSTRACT

Magnesium (Mg^{2+}) is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It is an important structural component of bone and soft tissue cells. The strict control of blood Mg^{2+} concentration is essential for many physiological processes such as cell permeability, neuronal activity, neurotransmitter release, muscle contraction, cardiac excitability, hormone receptor binding. Mg^{2+} has a fundamental role as a co-factor in more than 300 enzymatic reactions involving energy metabolism and synthesis of nucleic acids. A persistent hypomagnesemia is associated with severe health risks and is involved in the pathogenesis of type 2 diabetes mellitus, osteoporosis, heart and vascular diseases. Therefore, the tight regulation of plasma Mg^{2+} levels is of vital importance. Mg^{2+} homeostasis depends on three organs: the intestine, which determines Mg^{2+} uptake, bones that store Mg^{2+} and the kidneys, which are responsible for Mg^{2+} excretion.

***Key words**: magnesium homeostasis, magnesium channel*

INTRODUCTION

Magnesium (Mg^{2+}) is the fourth most abundant cation in the human body and the second most abundant intracellular cation. Mg^{2+} plays an essential physiological role in many functions of the body: it is important for bone mineralization, muscle contraction, neuronal activity, control of vascular tone, cardiac excitability, neurotransmitter release, hormone receptor binding and transmembrane ion flux [22]. Intracellular Mg^{2+} forms a key complex with ATP and has a key role in many other important biological processes such as protein synthesis, cell replication, and energy metabolism [14]. There are multifold clinical manifestations of an altered Mg^{2+} balance. Hypermagnesemia can cause neurologic and cardiac sequelae, including lethargy, confusion, coma, complete heart block, and cardiac arrest. Hypomagnesemia is associated with a wide spectrum of diseases, including type 2 diabetes, hypertension, osteoporosis and depressions [25]. Therefore, controlling and maintaining magnesium homeostasis is of vital importance.

MAGNESIUM INTAKE AND DISTRIBUTION

The normal adult human body contains approximately 22-24 g magnesium [22]. About 60% of the magnesium is present in the bones, 20% in skeletal muscles, 19% in other soft tissues, and less than 1% in the extracellular fluids. Intracellular magnesium concentrations range from 5 to 20 mmol/l: 1–5% is ionized, the remainder is bound to proteins, negatively charged molecules and adenosine triphosphate (ATP). Extracellular accounts about 1% of total body magnesium [20]. Approximately 55- 70% of plasma Mg^{2+} exists in the ionized, free, physiologically active form, which is important for its physiologic functions, 10-15 % is complexed with various anions such as phosphate and citrate and 20-30% is protein bound. Of the protein bound fraction, 60–70% is associated with albumin, and the rest is bound to globulins [11]. In healthy people, plasma magnesium is carefully regulated within the narrow range of 0.7-1.1 mmol/l. In order to maintain normal Mg^{2+} levels, the recommended daily dietary allowance is 6 mg/kg/day. This means 400 to 420 mg/day for adult men and 310-320 mg/day for adult women [1]. The daily requirement is higher in pregnancy, lactation and following debilitating illness. Magnesium intake depends on the magnesium concentration in drinking water and food composition. High amounts of magnesium are found in nuts, green leafy vegetables such as spinach and broccoli (which are rich in magnesium-

21. Halacheva L, Kolev N, **Kostov K**. Abnormal renal handling of magnesium. Science & Technologies. 2017; 7(1): 73-79. ISSN: 1314-4111

Science & Technologies

ABNORMAL RENAL HANDLING OF MAGNESIUM

Lyudmila Halacheva, Nikolai Kolev, Krasimir Kostov
Department of Physiology and Pathophysiology, Medical University – Pleven
l_halacheva@abv.bg

ABSTRACT

Magnesium (Mg^{2+}) is the fourth most abundant cation in the human body and the second most common cation in the intracellular fluid. The strict control of plasma Mg^{2+} level is essential for many physiological processes such as cell permeability, neurotransmitter release, muscle contraction, hormone receptor binding, neuronal activity and cardiac excitability. It has a fundamental role as a co-factor in more than 300 enzymatic reactions involving energy metabolism and synthesis of nucleic acids. Plasma Mg^{2+} concentration is tightly regulated by the dynamic balance and interplay between intestinal absorption, exchange from bone and renal reabsorption. The kidney plays a central role in maintaining magnesium homeostasis. The majority of filtered Mg^{2+} is reabsorbed in the thick ascending limb of the loop of Henle by a passive paracellular transport, mediated by tight junction proteins claudin-16 and -19. Their mutations result in increased urinary Mg^{2+} excretion and hypomagnesemia. The "fine-tuning" of Mg^{2+} reabsorption takes place along the distal convoluted tubules where Mg^{2+} is reabsorbed by an active transcellular transport via transient receptor potential channel melastatin 6 (TRPM6). This channel regulates the apical entry of magnesium into epithelia and alters whole-body magnesium homeostasis by controlling urinary excretion. TRPM6 is controlled by numerous factors and hormones at the level of transcription, membrane expression, and function.

Key words: *magnesium reabsorption, claudin-16/19, TRPM6, hypomagnesemia*

INTRODUCTION

Magnesium (Mg^{2+}) is the fourth most abundant cation in the human body and the second most common cation in the intracellular fluid. The precise control of plasma Mg^{2+} level is essential for many physiological processes such as cell permeability, neurotransmitter release, muscle contraction, hormone receptor binding, neuronal activity and cardiac excitability [29]. Magnesium has a fundamental role as a co-factor in more than 300 enzymatic reactions involving energy metabolism, synthesis of proteins and nucleic acids [26]. In healthy people, plasma magnesium is carefully regulated within the narrow range of 0,7-1,1 mmol/l. This article reviews the role of the kidneys in magnesium homeostasis and also discusses genetic and drug-induced causes of renal Mg^{2+} wasting.

MAGNESIUM REABSORPTION ALONG RENAL TUBULES

Approximately 70 - 80 % of total plasma Mg^{2+} (20-30% is protein bound) is filtered in the glomerulus, which accounts about 2000-2400 mg per day. Under normal conditions 95-97% of filtered magnesium is reabsorbed in the renal tubules and only 3-5% is excreted in the urine i.e.~100 mg [8]. 10-25% of the filtered magnesium is reabsorbed in the proximal tubule (PT). The exact mechanisms are not known, magnesium is believed to be absorbed via passive paracellular transport, facilitated by the increased intraluminal magnesium concentration, created by water uptake via aquaporin 1 (AQP1) [27].

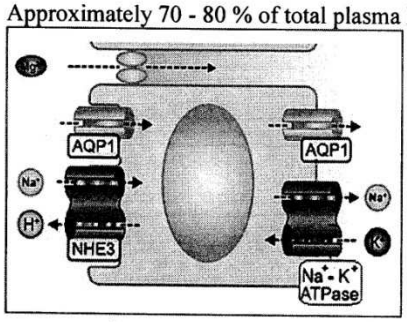

Figure 1. Mg^{2+} reabsorption in PT.

Mg^{2+} reabsorption mainly occurs in the late parts of the PT, where the concentration gradient is sufficient to favor the passive transport (fig. 1). Previous Na^+ reabsorption is

Резюмета на научните трудове за ОНС „Доктор“

22. **Kostov K**, Dimitrova A, Grigoryan A, Tisheva S, Ruseva A, Atanasova M, Gospodinov K, Blazhev A. Changes in the serum levels of endothelin-1, matrix metalloproteinases-2, -9 and C-reactive protein in patients with mild and severe degree of arterial hypertension. Comptes rendus de l'Academie bulgare des Sciences, Tome 67, No 3, 2014, 427-434. ISSN: 1310-1331, **НАЦИД, Web of Science Q4 IF$_{2014}$ 0.284, Scopus Q3 SJR$_{2014}$ 0.205**

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Tome 67, No 3, 2014

MEDECINE
Pathophysiologie

CHANGES IN THE SERUM LEVELS OF ENDOTHELIN-1, MATRIX METALLOPROTEINASES-2, -9 AND C-REACTIVE PROTEIN IN PATIENTS WITH MILD AND SEVERE DEGREE OF ARTERIAL HYPERTENSION

Krasimir Kostov, Anelia Dimitrova, Armine Grigoryan, Snejana Tisheva*, Adelaida Ruseva, Milena Atanasova***, Constantin Gospodinov*, Alexander Blazhev*****

(*Submitted by Corresponding Member R. Radomirov on October 21, 2013*)

Abstract

Haemodynamic stress in arterial hypertension leads to increased production of endothelin-1 (ET-1). Changes in the extracellular matrix are controlled largely by methalloproteinase-2 (MMP-2) and methalloproteinase-9 (MMP-9) which play an important role in vascular remodelling of hypertension. C-reactive protein (CRP) is an acute phase protein which is synthesized by hepatocytes under the effect of interleukin-6 (IL-6) in inflammation.

The purpose of the study was to investigate the relationship of ET-1, MMP-2, MMP-9 and CRP with the degree of arterial hypertension and the systemic and vascular inflammatory response.

Three groups were formed: group I – 31 patients with mild hypertension (MH); group II – 29 patients with severe hypertension (SH); group III – 15 persons in a control group (CG). ET-1 was determined by ELISA kit of "Biomedika", MMP-2 and MMP-9 by ELISA kit of the "R&D Systems", and the CRP – through immunoturbidimetric method with monoclonal anti-CRP antibodies. The analysis used the statistical program STATGRAPHICS.

This study was supported by Grant No 1/2012 of the Medical University of Pleven.

23. Kostov K, Dimitrova A, Tisheva S, Blazhev A, Atanasova M, Ruseva A, Tsinlikov I, Grigoryan A. Endothelin-1 in patients with arterial hypertension and type 2 diabetes mellitus. Science & Technologies, Volume IV, Number 1, 2014, Medicine, 420-424. ISSN: 1314-4111

ЕНДОТЕЛИН-1 ПРИ ПАЦИЕНТИ С АРТЕРИАЛНА ХИПЕРТЕНЗИЯ И ЗАХАРЕН ДИАБЕТ ТИП 2

Красимир Костов[1], Анелия Димитрова[1], Снежана Тишева[2], Александър Блажев [3], Милена Атанасова[3], Аделаида Русева[4], Иван Цинликов[5], Армине Григорян[1]
[1]Катедра „Физиология и патофизиология",
[2]Катедра „Кардиология, пулмология и ендокринология",
[3]Катедра „Анатомия, хистология, цитология и биология",
[4]Катедра „Клинична лаборатория, клинична имунология и алергология",
[5]Катедра „Пропедевтика на вътрешните болести"
МУ-Плевен, ул. „Климент Охридски" №1, 5800 Плевен, България
e-mail: dr.krasi_kostov@abv.bg

ENDOTHELIN-1 IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS

Krasimir Kostov[1], Anelia Dimitrova[1], Snejana Tisheva[2], Aleksander Blazhev, Milena Atanasova[3], Adelaida Ruseva[4], Ivan Tsinlikov[5], Armine Grigoryan[1]
[1]Department of "Physiology and Pathophysiology",
[2]Department of "Cardiology, Pulmonology and Endocrinology",
[3]Department of "Anatomy, Histology, Cytology and Biology",
[4]Department of "Clinical Laboratory, Clinical Immunology and Allergology",
[5]Department of "Propaedeutics of Internal diseases"
Medical University of Pleven, 1"Kliment Ohridski" Str., 5800 Pleven, Bulgaria
e-mail: dr.krasi_kostov@abv.bg

ABSTRACT

The role of endothelin-1 (ET-1) in arterial hypertension has been established through measurement of its serum levels. Although some studies have demonstrated an increase of ET-1 in hypertensive patients, others show normal or lightly elevated levels. In patients with type 2 diabetes mellitus (T2DM), the disease is often combined with arterial hypertension, which leads to a more severe complications of diabetes. ET-1, which is a powerful vasoconstrictor with proliferative, profibrotic and proinflammatory properties, may contribute through various mechanisms to the development of diabetic vascular diseases and hypertension. Furthermore ET-1 causes a reduction in insulin sensitivity and may so participate in the development of the metabolic syndrome. The objective of the study was to compare the serum concentrations of ET-1 in patients with mild and severe degree of arterial hypertension with and without T2DM with those of normotensive individuals without DM. The survey results show that in patients with arterial hypertension with and without T2DM, the levels of ET-1 are higher than those of the control group. The average levels of ET-1 in patients with arterial hypertension with T2DM are significantly increased compared with those in patients with arterial hypertension without DM.

Key words: *endothelin-1, arterial hypertension, type 2 diabetes mellitus*

ВЪВЕДЕНИЕ

Хемодинамичният стрес при артериална хипертензия води до повишена продукция на ET-1, който е един от най-силните открити до момента вазоконстриктори [4]. Неговото действие е от 30 до 50 пъти по-силно от това на норадреналина и ангиотензин II (AT II) [1] и между 8-110 пъти по-слабо от това на уротензин II (U-II) [8,9]. Генерира се основно от ендотелните клетки. Концентрациите на ET-1 в съдовата стена са над 100 пъти по-високи от циркулиращите му плазмени нива. Така ET-1 действа основно като автокринен/паракринен

24. Kostov K, Rashev T, Dimitrova A, Tisheva S, Blazhev A, Atanasova M, Gospodinov K. Endothelin-1, cardiotrophin-1, galectin-3, MMP-1 and TIMP-1 as biomarkers of cardiovascular risk in patients with arterial hypertension, Science & Technologies, Volume V, Number 1, 2015, Medicine, 178-183. ISSN: 1314-4111

ЕНДОТЕЛИН-1, КАРДИОТРОФИН-1, ГАЛЕКТИН-3, МАТРИКСНА МЕТАЛОПРОТЕИНАЗА-1 И ТЪКАННИЯ ИНХИБИТОР НА МЕТАЛОПРОТЕИНАЗИТЕ-1, КАТО БИОМАРКЕРИ ЗА СЪРДЕЧНО-СЪДОВИЯ РИСК ПРИ ПАЦИЕНТИ С АРТЕРИАЛНА ХИПЕРТЕНЗИЯ

Красимир Костов[1], Тихомир Рашев[2], Анелия Димитрова[1], Снежана Тишева[3], Александър Блажев[4], Милена Атанасова[4], Константин Господинов[3]
[1]Катедра „Физиология и патофизиология",
[2]Сектор „Молекулярна билогия" - лаборатория за научни изследвания,
[3]Катедра „Кардиология, пулмология и ендокринология",
[4]Катедра „Анатомия, хистология, цитология и биология",
МУ-Плевен, ул. „Климент Охридски" №1, 5800 Плевен, България
e-mail: dr.krasi_kostov@abv.bg

ENDOTHELIN-1, CARDIOTROPHIN-1, GALECTIN-3, MATRIX METALLOPROTEINASE-1 AND TISSUE INHIBITOR OF METALLOPROTEINASES-1 AS BIOMARKERS OF CARDIOVASCULAR RISK IN PATIENTS WITH ARTERIAL HYPERTENSION

Krasimir Kostov[1], Tihomir Rashev[2], Anelia Dimitrova[1], Snejana Tisheva[3], Aleksander Blazhev[4], Milena Atanasova[4], Konstantin Gospodinov[3]
[1]Department of "Physiology and Pathophysiology",
[2]Sector "Molecular Biology" - Laboratory for research,
[3]Department of "Cardiology, Pulmonology and Endocrinology",
[4]Department of "Anatomy, Histology, Cytology and Biology",

Medical University of Pleven, 1"Kliment Ohridski" Str., 5800 Pleven, Bulgaria
e-mail: dr.krasi_kostov@abv.bg

ABSTRACT

The prevalence of hypertension is increasing worldwide and heart failure as a result of hypertensive heart disease, would soon be become the most common cause of heart failure. Search for suitable biomarkers of inflammation and fibrosis, can identify these patients who are with higher risk for progression from latent to symptomatic heart failure. Timely detection and treatment of these patients would reduce the future cardiovascular risk, earlier debilitating condition, and the costs of hospitalization, medical cares and expensive therapy. Such biomarkers in patients with arterial hypertension may be: ET-1, CT-1, Gal-3, MMP-1 and TIMP-1.

Key words: *arterial hypertension, endothelin-1,* cardiotrophin-*1,* galectin-3, *MMP-1, TIMP-1*

УВОД

Разпространението на артериалната хипертензия се увеличава в световен мащаб и сърдечната недостатъчност вследствие на хипертензивните сърдечни заболявания (hypertensive heart disease- HHD), скоро ще се превърне в най-честата причина за сърдечна недостатъчност (СН). Търсенето на подходящи биомаркери на възпалителния процес и последващата фиброза в съдовете и сърцето, може да идентифицира тези пациенти, които са с най-висок риск за прогресия от латента към симптомна СН. Своевременното откриване и лечение на тези пациенти би намалило бъдещия сърдечно-съдов риск, ранното им инвалидизиране, както и разходите за хоспитализация, медицински грижи и скъпо струваща терапия. Въпреки важността на проблема, търсенето на специфични биомаркери при артериална хипертензия изостава в сравнение с други заболявания. Определението на

25. Костов К, Григорян А, Димитрова А. Ендотелини и артериална хипертензия. Сборник „Наука и младост" 2012, МУ- Пловдив, 223-231. ISSN: 1314-9229

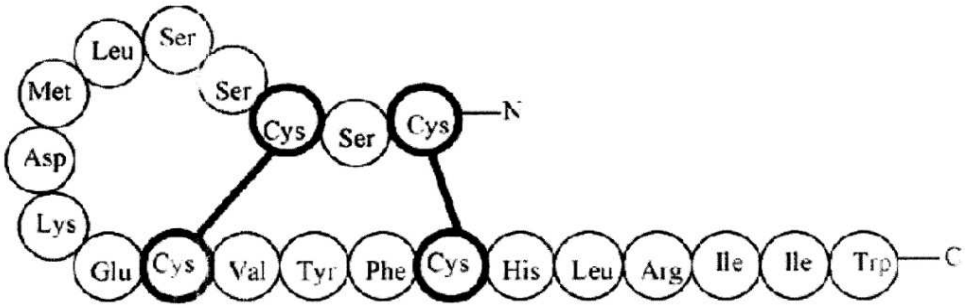
ЕНДОТЕЛИНИ И АРТЕРИАЛНА ХИПЕРТЕНЗИЯ

Красимир Костов, Армине Григорян, Анелия Димитрова
Катедра „Физиология и патофизиология",
Факултет по медицина, Медицински университет - Плевен

I. Ендотелини и техните патофизиологични ефекти върху различните органи и системи.

1. Ендотелини.

През 1985 г. Hikey и сътр. публикуват доклад, който описва съществуването на ендотелен контрактилен фактор. Впоследствие Masashi Yanagisawa и Hiroki Kurihara, заедно със Sadao Kimura и Katsutoshi Goto, започват работа по изолирането на това вещество. През1988 г. този фактор е успешно пречистен и идентифициран, като нов пептид означен с наименованието - ЕНДОТЕЛИН, поради ендотелния си произход.(1, 2)



Фиг. 1. *Структура на ЕТ-1*
ЕТ-1 съдържа 21 АК и 2 дисулфидни връзки Cys1-Cys15 и Cys3-Cys11, както и хидрофобен С-терминал Trp 21.

Семейството на ендотелините включва три изоформи, които се означават като ЕТ-1, ЕТ-2, ЕТ-3, състоят се от 21 аминокиселини и съдържат по две дисулфидни връзки в молекулата си.(фиг.1) ЕТ-1 е с молекулно тегло 2492 D и се кодира от ген, който се намира в хромозома 6. Кодиращият ген на ЕТ-2 се намира в хромозома 1. ЕТ-2 съдържа две замествания на АК и има 90% хомоложни последователности с ЕТ-1. Кодиращият ген на ЕТ-3 се намира в хромозома 20. ЕТ-3 съдържа шест замествания на АК и има 71% хомоложни последователности с ЕТ-1 и ЕТ-2.

Най-важно значение от трите ендотелни пептида има ЕТ-1. (3, 4)

Ендотелин-1 е най-мощният вазоконстриктор открит досега. Неговото действие е от 30 до 50 пъти по-силно от това на норадреналина и ангиотензин II (ATII) (5). Генерира се

26. Костов К, Григорян А, Димитрова А, Тишева С, Русева А, Атанасова М, Господинов К, Блажев А. Ендотелин-1 и матриксни металопротеинази-2 и 9 при пациенти с различна степен на артериална хипертензия. Сборник „Наука и младост" 2013, МУ-Пловдив, 85-90. ISSN: 1314-9229

Ендотелин-1 и матриксни металопротеинази-2 и 9 при пациенти с различна степен на артериална хипертензия

К. Костов[1], А. Григорян[1], А. Димитрова[1], С. Тишева[2], А. Русева[3], М. Атанасова[4], К. Господинов[2], А. Блажев[4]

[1]Катедра „Физиология и патофизиология", Сектор „Патофизиология"
[2]Катедра „Кардиология, пулмология и ендокринология", Клиника по „Кардиология"
[3]Катедра „Клинична лаборатория, клинична имунология и алергология", ЦКЛ
[4]Катедра „Анатомия, хистология, цитология и биология", Сектор „Биология"
Медицински университет – Плевен

e-mail: dr.krasi_kostov@abv.bg

Въведение

Хипертонията е многофакторно заболяване, което е свързано с патологични промени в нервните, бъбречните, хормоналните и съдовите механизми за контрол на кръвното налягане. Най-важната регулация се осъществява на нивото на ендотела чрез отделяне на вазодилататорни (азотен оксид – NO, простациклин – PGI_2, endothelium-derived hyperpolarizing factor – EDHF) и вазоконстрикторни вещества, като: ендотелин-1 (ЕТ-1), тромбоксан A_2 (TxA_2), ангиотензин II (АТ II). Нарушеният баланс между тях, води до трайно повишаване на съдовия тонус и структурни промени в съдовата стена (1).

Хемодинамичният стрес води до повишена продукция на ЕТ-1, който е един от най-силните открити до момента вазоконстриктори. Неговото действие е от 30 до 50 пъти по-силно от това на норадреналина и АТ II (2) и между 8-110 пъти по-слабо от това на уротензин II (U-II) (3, 4). Генерира се основно от ендотелните клетки. Концентрациите на ЕТ-1 в съдовата стена са над 100 пъти повисоки от циркулиращите му плазмени нива. Така ЕТ-1 действа основно като автокринен / паракринен пептид, а не като циркулиращ хормон (5). Освен в ендотела, ЕТ-1 се произвежда в сърцето, бъбреците, надбъбречната жлеза, задния дял на хипофизата и ЦНС, макар и в изключително ниски концентрации (6).

ЕТ-1 взаимодейства с два типа ендотелинови рецептори: ЕТА и ЕТВ. Те представляват G-protein свързани трансмембранни белтъци. Въз основа на своите in vivo фармакологични ефекти, ЕТВ-рецепториторите се класифицират в два подтипа – ЕТВ1 и ЕТВ2. ЕТА-рецепторите се експресират предимно в съдовите гладкомускулни клетки и кардиомиоцитите. Ефектите свързани с ЕТА-рецептора водят до засилена Ca^{2+} мобилизация в гладкомускулните клетки на съдовете и вазоконстрикция. ЕТВ-рецепторите се експресират предимно върху съдовите ендотелни клетки. ЕТВ-рецепторната стимулация и по-специално тази на ЕТВ1 – рецептора, активира сигнални пътища, които водят до освобождаване на релаксиращи фактори като NO, PGI2 и EDHF (1,2). ЕТВ2 – свързаният отговор е вазоконстрикция, подобно на действието на ЕТА рецептора. През последните години се натрупаха и неопровержими доказателс-

27. Костов К, Димитрова А, Тишева С, Русева А, Атанасова М, Блажев А, Григорян А, Господинов К. Роля на магнезия в патогенезата на артериалната хипертензия. Сборник „Наука и младост" 2014, МУ-Пловдив, 114-120. ISSN: 1314-9229

Роля на магнезия в патогенезата на артериалната хипертензия

Красимир Костов[1], Анелия Димитрова[1], Снежана Тишева[2], Аделаида Русева[3], Милена Атанасова[4], Александър Блажев[4], Армине Григорян[1], Константин Господинов[2]

[1]Катедра „Физиология и патофизиология", Сектор „Патофизиология"
[2]Катедра „Кардиология, пулмология и ендокринология", Клиника по кардиология
[3]Катедра „Клинична лаборатория, клинична имунология и алергология", ЦКЛ
[4]Катедра „Анатомия, хистология, цитология и биология", Сектор „Биология"
Медицински университет – Плевен

e-mail: д-р Красимир Костов – dr.krasi_kostov@abv.bg

Въведение

Магнезият (Mg^{2+}) е вторият най-разпространен вътреклетъчен катион и е кофактор в над 300 ензимни реакции. Участва в множество процеси регулиращи сърдечно-съдовата функция (1,2). При нормални физиологични условия нивата на Mg^{2+} в серума се поддържат в границите на тесен референтен диапазон – 0,7 до 1,1 mmol/l, което се осъществява чрез строг контрол върху стомашно-чревната абсорбция и бъбречната му секреция (1). Малки промени в екстрацелуларната и интрацелуларната Mg^{2+} концентрация може да имат значителен ефект върху съдовия тонус, еластичност и растеж (3). Магнезиевият транспорт се осъществява чрез два основни механизма – трансцелуларен и парацелуларен (4). Трансцелуларният транспорт включва инфлуксни и ефлуксни транспортни системи. Mg^{2+} инфлукс се контролира от редица транспортери, като Mrs2p, SLC41A1, ACDP2, Mag T1, както и от специализирани катионни канали – TRPM6 и TRPM7 (transient receptor potential melastatin -6 и -7 cation channels) (5). TRPM6 се експресира главно в бъбреците и цекума, където регулира Mg^{2+} реабсорбция. TRPM7 се експресира повсеместно и неговата липса е летална (1). Mg^{2+} ефлукс се осъществява чрез Na^+-зависими и Na^+-независими пътища (5). В Mg^{2+} транспорт участват и Na^+/Mg^{2+} и Mg^{2+}/Ca^{2+} помпа (1). Парацелуларният транспорт на Mg^{2+} е пасивен процес, който се осъществява през плътните междуклетъчни контакти на епителните клетки в интестиналния тракт и бъбреците. Той зависи от специални структурни белтъци – клаудини. Чревното усвояване на Mg^{2+} е свързано с относително ниската експресия на „затягащи" клаудини 1, 3, 4, 5 и 8. В бъбреците парацелуларния Mg^{2+} транспорт зависи основно от клаудини 16 (paracellin-1) и 19 (4).

Промените в нивата на Mg^{2+} могат да допринесат за патофизиологията на хипертензията (3). Mg^{2+} играе важна роля в регулацията на артериалното налягане, като модулира съдовия тонус и реактивност (6) чрез различни механизми:

1) Нарушенията на Mg^{2+} транспорт могат да предразположат към развитие на хипертензия и последващи сърдечно-съдови заболявания (5). Макар и оскъдни, данните докладвани до момента показват потенциалната регулаторна роля

28. Костов К, Григорян А, Димитрова А, Тишева С, Русева А, Атанасова М, Господинов К, Блажев А. Серумен магнезий и матриксни металопротеинази-2 и -9 (ММР-2 и ММР-9) при пациенти с лека и тежка степен на артериална хипертензия. Сборник доклади и резюмета от XII национална научна сесия за студенти и преподаватели, МУ- Плевен, 2014, 269-276. ISBN: 978-954-756-150-2

СЕРУМЕН МАГНЕЗИЙ (Mg^{2+}) И МАТРИКСНИ МЕТАЛОПРОТЕИНАЗИ-2 И -9 (ММР-2 И ММР-9) ПРИ ПАЦИЕНТИ С ЛЕКА И ТЕЖКА СТЕПЕН НА АРТЕРИАЛНА ХИПЕРТЕНЗИЯ

К. Костов[1], А. Григорян[1], А. Димитрова[1], С. Тишева[2], А. Русева[3], М. Атанасова[4], К. Господинов[2], А. Блажев[4]

[1]Катедра „Физиология и патофизиология"
[2]Катедра „Кардиология, пулмология и ендокринология"
[3]Катедра „Клинична лаборатория, клинична имунология и алергология"
[4]Катедра „Анатомия, хистология, цитология и биология", Сектор „Биология"
Сектор „Патофизиология"
Катедра „Физиология и патофизиология", МУ-Плевен

Резюме

Въведение: Магнезият е естествен антагонист на йоните на калция. Той модулира съдовия тонус и реактивност чрез промяна на отговорите към редица вазоконстрикторни и вазодилататорни агенти. В сърдечно-съдовата система промените на екстрацелуларния матрикс се контролират от MMPs и техните тъканни инхибитори- TIMPs. ММР-2 , ММР-9 и TIMP-1 играят важна роля за съдовото ремоделиране при хипертензия.

Цел: Настоящото изследване има за цел да проучи серумните концентрации на Mg^{2+}, ММР-2 и ММР-9 при пациенти с различна степен на артериална хипертензия.

Методи: Сформирани бяха три групи: I група- 31 пациента с лека хипертензия (ЛХ); II група- 29 пациента с тежка хипертензия (ТХ); III група- 15 здрави лица, контролна група (КГ). ММР-2 и ММР-9 са определени чрез ELISA kit на „R&D Systems", а серумният Mg^{2+}- чрез количествен колориметричен метод. За анализите е използвана статистическа програма STATGRAPHICS.

Резултати: Установи се, че съществувт статистически значими разлики в серумните концентрации на Mg^{2+} (mmol/l), между ЛХ спрямо КГ (p=0,0145) и между ЛХ спрямо ТХ (p=0,0187). Има също статистически значими разлики между концентрациите на ММР-9 (ng/ml) при ТХ спрямо КГ (p=0,0010), както и между ЛХ спрямо ТХ (p=0,0006). Съществува обратна корелационна зависимост между нивата на серумния Mg^{2+} и ММР-2 в групата с ТХ (p= 0,0340).

Обсъждане: Серумните концентрации на Mg^{2+} са по-високи при пациентите с ЛХ и ТХ в сравнение с КГ. Нивата на ММР-9 намаляват с нарастване степента на хипертензията в следния порядък: КГ>ЛХ>>ТХ, като при ТХ те са понижени почти двойно в сравнение с КГ. ММР-2 не показва специфични промени при различните степени на хипертензия.

Ключови думи: артериална хипертензия, магнезий, металопротеинази -2 и -9

Въведение. Магнезият е вторият най-разпространен вътреклетъчен катион в организма и е кофактор в над 300 ензимни реакции.Участва в множество процеси