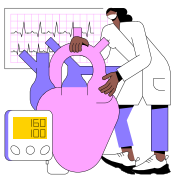
ISBN: 978-93-26254-35-8

THERAPY AND PREVENTION METHODS FOR ESSENTIAL ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS



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Published by
Novateur Publication
466, Sadashiv Peth, M.S.India-411030
novateurpublication.org

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THERAPY AND PREVENTION METHODS FOR ESSENTIAL ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

Monograph

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The monograph is devoted to the actual problem of pediatric cardiology – essential arterial hypertension in children. Numerous scientific and applied research and practical developments in the aspects of risk factors, the course of diagnosis, method of treatment and prevention of essential arterial hypertension in children and adolescents were analyzed and summarized. Special emphasis is placed on diagnostic methods, methods of treatment and prevention of endothelial dysfunction in the development of essential arterial hypertension in children. The presented data expand the understanding of the mechanisms of the process of development of stable hypertension at the level of vascular endothelium, autonomic nervous system, and immune system in children. The criteria for the diagnosis of endothelium–dependent risk factors for the development of essential arterial hypertension in children based on associations of clinical, hemodynamic and immunological parameters are recommended. These diagnostic criteria made it possible to develop a method for the treatment and prevention of endothelial dysfunction in essential arterial hypertension in children and adolescents in primary health care.

CONTENTS

PREFACE

Essential arterial hypertension (EAH) is the most common cardiovascular disease (CVD) and one of the most urgent medical problems worldwide. According to statistics from the World Health Organization (WHO), the main causes of death from non-communicable diseases (NCDs) are CVD (48%); ... in 2016, 17.9 million people died from them; ... 13% of all deaths globally are due to high blood pressure (BP). Elevated blood pressure is the cause of 51% of deaths from stroke and 45% from coronary heart disease …[1]. The origins of adult EAH lie in childhood. From 40% to 65% of elevated blood pressure in children pass into ischemic and hypertensive diseases of adults. EAH in children is of particular relevance in view of its high prevalence rate, untimely diagnosis and lack of prevention.

Numerous clinical studies are conducted in the world aimed at studying the clinical and immunological factors of the development of essential arterial hypertension and improving its diagnosis, treatment, and prevention. In this regard, clinical studies devoted to EAH in children are of particular relevance to study the prevalence, risk factors and assessment of the clinical course; to determine the parameters of vegetative homeostasis and signs of systemic inflammation; to study hemodynamic and biochemical markers of endothelial dysfunction, a genetic prerequisite for the development of the disease; to ensure the effectiveness of treatment, set of preventive measures that improve the quality of life of patients; to develop pathogenetically sound methods of diagnosis, treatment, and prevention.

In our country, special attention is paid to the social protection of the population and the improvement of the health care system, in particular. Close attention is paid to early diagnosis, prevention and reduction of the frequency of complications of diseases in children. The package of measures to improve the health care system includes "... introduction of the requirements of clinical protocols of standards and recommendations of WHO on arterial hypertension into practice of all primary health care institutions of the Republic."[2] In this direction the strengthening of children's health, especially the development of high modern methods of early diagnosis and treatment of CVD in children is becoming important.

According to foreign authors, on average from 0.7% to 33.0% of adolescent children suffer from EAH, and in recent years there has been a tendency to increase the incidence in developed countries of Europe, the USA, and Japan. Based on systematic reviews and meta-analyses it is possible to see certain trends that showed the heterogeneity of the analyzed samples of sick children, and consequently less

[1] World Health Organization [Internet].United Nations to establish WHO-led interagency Task Force on the Prevention and Control of Noncommunicable Diseases. Geneva: WHO; 2013. Available from: http://www.who.int/dg/mediacentre/news/notes/2013/ncds_ecosoc_20130 [accessed 5 August 2013].

definite results in the diagnosis and prevention of EAH in children. To date the recommendations of the European Society of Hypertension and the European Society of Cardiology on the control of arterial hypertension (AH) in children and adolescents (2009) are in effect; the Practical recommendations on screening and management of high blood pressure in children and adolescents of the American Pediatric Academy (2017) have been updated. In the Russian Federation the recommendations for the diagnosis, treatment, and prevention of hypertension in children and adolescents were revised in accordance with the Recommendations of the European Society of Hypertension (2009). In the Republic of Uzbekistan nowadays methods of diagnosis, treatment, and prevention of EAH in children are at the stage of development.

Aspects of the pathogenesis of EAH are not fully disclosed, and the trigger mechanisms of endothelial dysfunction (ED), as one of the main factors associated with EAH, need to be detailed. The roles of nitric oxide, endothelin and cytokines as important markers of ED are shown. The authors conclude that the severity of endothelial dysfunction affects the severity of the clinical manifestation of the disease. The study of endothelium-dependent risk factors for the development of EAH in children will optimize the diagnosis of EAH, as well as its primary and secondary prevention.

INTRODUCTION

The WHO World Health Statistics 2012 report focused on the growing problem of the burden of non-communicable human diseases stating: "...The main causes of death from NCDs are cardiovascular diseases (CVD) (48%). ... It is expected that the number of deaths from CVD will increase annually from 17 million people in 2008 to 25 million in 2030 ..." (World health statistics 2012). Essential arterial hypertension (EAH) is one of the most common diseases of the cardiovascular system. It was found that 20-30% of the adult population suffer from EAH and with age this rate increases, reaching 50-65% in people over 65 years of age. There is no doubt that the origins of EAH in adults are in childhood. The severity of the problem is also supported by EAG high prevalence rate in children and adolescents, ranging from 2.4% to 18% (Baranov A.A., 2012, Sadykova D.I., Sergeeva E.V., 2014), and according to the results of foreign authors from 0.7% to 33% (Bucher B.S., et al. 2013, Litwin M., 2013). It is notably, that 40-65% of them have a progressive course with a high probability of further transformation of arterial hypertension into ischemic and hypertensive diseases in adults. In recent years there has been a clear trend towards a further increase in this disease prevalence rate in children and adolescents. In this connection, the medical care of children and adolescents with EAH becomes a matter of particular concern.

Currently, special attention in the development of EAH in children and adolescents is paid to the function of endothelium. Violation of endothelial function with the development of endothelial dysfunction is an early sign of EAH. The analysis of modern literature allows us to systematize the evidence that endothelial dysfunction (ED) is one of the key pathogenetic mechanisms of the development of CVD, including EAH. The endothelial monolayer of cells lines the inner surface of blood vessels and heart valves and is a highly specialized and metabolically active link between circulating blood and smooth muscle cells. The concept of ED pathogenesis is based on imbalance between vasoconstrictor and vasodilating endothelial factors in favor of vasoconstrictors that induce the proliferation of vascular smooth muscle cells and cardiomyocytes. This pathophysiological process is the main mechanism of stabilization and progression of arterial hypertension. With ED the synthesis of the endothelium–dependent relaxing factor nitric oxide (NO) decreases and production of counterparty NO - endothelin -1 (ET-1) increases. ET-1 synthesized in the endothelium is the most powerful vasoconstrictor peptide and a marker of atherosclerosis and ED [22, 33]. One of the most active pressor substances ET-1 can directly lead to increase in blood pressure and participate in the remodeling of the heart and blood vessels [73].

Until now epidemiological and observational studies have proven that vitamin D deficiency (<20 ng/ml or <50 nmol/L 25 (OH)D) in blood serum is associated with CVD and arterial hypertension [68]. Also, an association has been established between insufficient, deficient levels of vitamin D provision in the body and the occurrence of ED [105, 106]. Therefore, timely elimination of this condition will prevent more severe consequences of the disease with decrease in mortality rate in the adult period [82].

The current treatment and prevention regimens for EAH in children and adolescents do not allow achieving the desired effect. In this regard, ED becomes the new goal of therapy and prevention of hypertension.

All of the above indicates the need to create a method for the treatment and prevention of EAH in children and adolescents based on the correction of vitamin D and ED levels with the background rational DASH diet and appropriate physical activity.

CHAPTER I. PROGNOSTIC SIGNIFICANCE OF INFLAMMATORY FACTORS IN THE DEVELOPMENT OF ESSENTIAL ARTERIAL HYPERTENSION IN CHILDREN

A very complex and multifunctional organ, the endothelium performs immune, vasoconstrictor, and vasodilator functions. The endothelium, on the one hand, participates in almost all processes defined as homeostasis and inflammation. On the other hand, it is the first target organ that implements many links of the pathogenesis of various diseases, including cardiovascular diseases [4, 35, 61, 113]. Endotheliocytes, due to their unique location, are the first to be met on the path of damaging factors, as a result of which their structure is disrupted and endothelial dysfunction (ED) develops. Since 1998 ED has become an urgent interdisciplinary problem after the discovery by Professors F. Muradou, R. Ferggott and L. Ignarro of the signal molecule nitric oxide in the regulation of the cardiovascular system. They were awarded the Nobel Prize in Medicine [12]. Nitric oxide is the main vasodilator. Processes such as oxidative stress, synthesis of vasoconstrictors, cytokines, and inflammatory factors that affect the occurrence and development of ED have an inhibitory effect on its production. ED always precedes damage or malfunction of any vessel, regardless of its organ localization. This applies to arteries, veins, as well as all structural components of the microcirculation system. Cellular activation and apoptosis lead to morphological changes in endotheliocytes, changes in the rheological properties of blood, stimulate platelet adhesion and aggregation, and cause the endotheliocytes themselves to peel off. Besides that, the integrity of the intercellular contacts of endotheliocytes is violated. At the same time, the permeability of the endothelium to lipoproteins and monocytes increases and the development of atherosclerotic damage to the vascular endothelium begins [].

We examined 408 schoolchildren in Tashkent, and 132 of them aged 13-16 years old (average age 14.64±0.19) selected randomly were subjected to further prospective observation.

The WHO recommendations and Russian recommendations (second revision, 2009) were taken as criteria for increased blood pressure and the diagnosis of essential arterial hypertension (EAH) [16].

***Clinical study inclusion criteria*:**

Children with stage I essential arterial hypertension (EAH) without target organ damage and children with normal and high normal blood pressure without exacerbation of chronic foci of infections for 6 months. The inclusion criteria were as follows: normal blood pressure, when SAP and DAP, the level of which is ≥the 10th and <90th percentile of the BP distribution curve in the population for the

corresponding age, gender and height; high normal BP, when the average values of SAP and/or DAP on three visits of ≥90th percentile, but <95th percentile for a given age, gender and height, or ≥120/80mmHg (even if this value is <90th percentile). AH I stage, when the average levels of SAP and/or DAP from three measurements are equal to or exceeding the values of the 95th percentile established for this age group, provided that they exceed the 99th percentile by no more than 5 mmHg (Russian Recommendations, 2009) [16]. Provided that the elevated blood pressure level is not constantly recorded during dynamic observation, labile hypertension is diagnosed. The age of children is 13-16 years old.

***Clinical study exclusion criteria**:*

The exclusion criteria were congenital anomalies of the kidneys, endocrine pathology, secondary or symptomatic hypertension, stage II EAH, and somatic pathology in acute stage.

In accordance with the goal and objectives of the study, the distribution of children into groups was carried out taking into account the following blood pressure indicators: group 1 were children with normal blood pressure (BP) (control group) (n=43), group 2 were 42 children with high normal blood pressure (HNBP) (comparative 2nd group), and 2 main groups: group 3 including 25 children with labile arterial hypertension (LAH) and group 4 with 22 children with stable arterial hypertension (SAH).

General characteristics of followed children according to the gender and age are presented in Table 1.

In the examined children groups there were 86 (65,2±4,1%) boys, and, correspondingly, 46 (34,8±4,1%) girls. Distribution according to the gender and average age was equal.

Table 1

General characteristics of gender and age the examined children

Gender	I group (control) with normal AP n=43		II group comparative with HNAP n=42		III group (1st basic) LAH n=25		IV group (2nd basic) SAH n=22	
	abs	%	abs	%	abs	%	abs	%
Girls	20	15.2±3.1	9	6.8±2.2	7	5.3±1.9	10	7.6±2.4
Boys	23	17.4±3.3	33	25.0±3.8	18	13.6±2.98	12	9.1±2.5
Average age	14.54±0.44		14.74±0.12		14.56±0.19		14.70±0.16	

We have conducted comprehensive studies using standard research methods (questionnaires, collection of ante- and postnatal anamnesis, study of heredity, environmental and psychological factors, clinical and paraclinical examination (measurement of blood pressure (BP); anthropometry according to the criteria of the World Health Organization (WHO, 2007) [37]; determination of the stage of puberty according to Tanner (1962) et al scheme).

Special attention was paid to the following [16]:

- complaints (headache, vomiting, insomnia);
- AP level and duration of AH;
- pregnancy and birth pathologies (preterm birth);
- young age pathology (immaturity, fetal hypotrophy, low fetal body weight);
- cerebro-cranial trauma and abdominal trauma;
- preterm puberty (development of secondary sexual traits in girls < 8 years old and in boys < 10 years old);
- pyelonephritis (possibly according to the cases of non-motivated body temperature rise, leukocyturia in history, dysuria);
- nutrition, excessive consumption of salt (habitual adding salt to ready food);
- changes in body mass (BM):
- level and character of physical activity (regular or periodical attendance of PE classes at school, training at sport clubs);
- smocking, non-steroid anti-inflammatory drugs;
- heredity burdened with HD, other CVD and DM (these diseases in parents under 55 years old);

In physical examination of children we assessed the following:

- anthropometric parameters such as height, weight and BMI. Calculation of BMI was done in compliance with the formula: body mass (kg/height, m^2). For the comparative assessment of height, weight and BMI of the children dependent on gender and age we calculated Z-scores in compliance with the method, proposed by the WHO (2007) [37], with evaluation of its clinical significance.

Up to date, it has been established that immune system inflammation is one of the main mechanisms of the development of cardiovascular pathology [79, 94]. C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) are associated with a high risk of complications in cardiac pathology and are considered as immunological markers of cardiovascular risk [41]. In this regard, at this stage of research, we analyzed the levels of highly sensitive C-reactive protein (CRPhs), tumor necrosis factor -α (TNF-α) and anti-inflammatory cytokine - interleukin – 10.

The level of highly sensitive CRP (CRP-hs) was determined in blood serum using Siemens (Germany) reagent kits on a Dimension EXL200 device, Siemens, Germany. The values of 0-3.0 mg/L are taken as the reference level of CRP-hs.

Concentrations of TNF-α and IL-10 levels in blood serum were determined using commercial kits "Vector-Best" (Russia) on the analyzer "Stat Fax 2100" (Israel) according to the methodology of quantitative enzyme solid-phase analysis ELISA.

The averaged parameters of the CRPhs level are shown in Figure 1. The highest level of CRP-hs was found in children with stable hypertension with a significant difference compared to the control ($p<0.05$). Significantly elevated values were also noted in the children with LAH ($p<0.05$) and HNAP ($p<0.05$) in relation to the parameters of children with normal blood pressure. The range of individual CRPhs values was large and varied from 0.01 to 4.71 mg/l.

A critical assessment of the potentially adverse effect of CRPhs in blood serum when predicting the risk of EAH development in children involves solving the question of the validity of this diagnostic test. At the same time, the validity of each specific test is determined by two fundamental operational characteristics, namely, sensitivity (sensitivity, Se) and specificity (specificity, Sp).

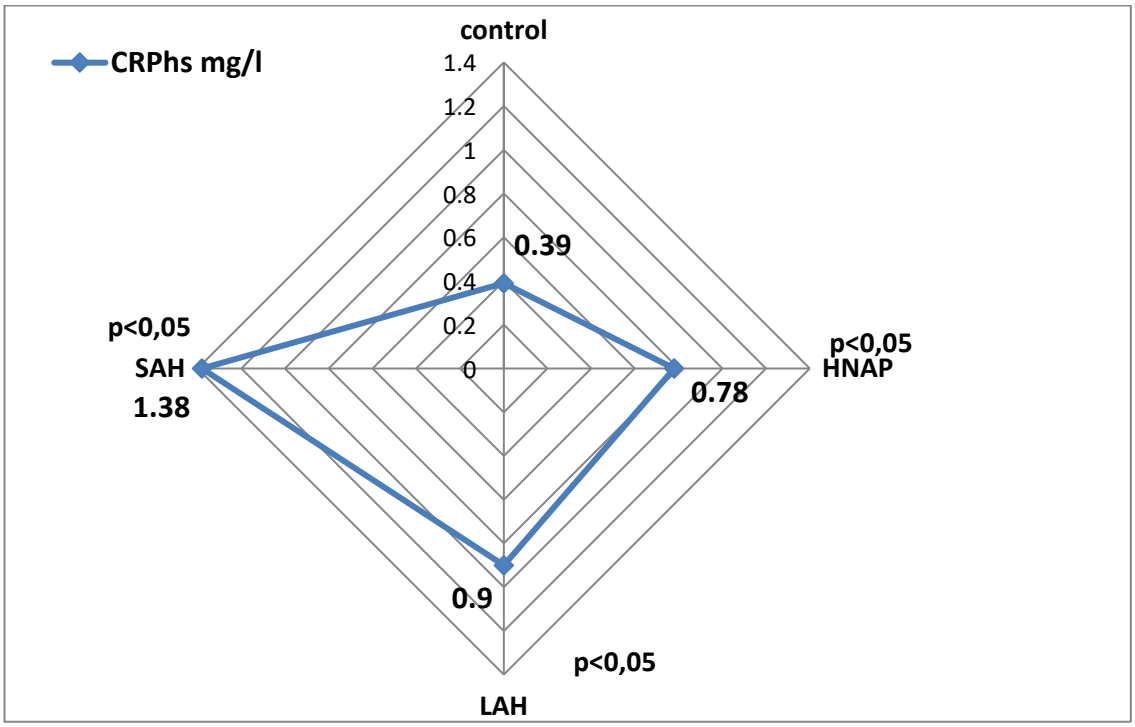

Figure 1. Average values of CRPhs in blood serum in the children of analyzed groups

For the group of children with HNAP the level of CRPhs>1.19 mg/L had moderate (Se=78.6%) sensitivity. Consequently, in 21.4% of the cases there is a probability that children who have a very high risk of developing the disease it will be classified as low. At the same time, this factor has a high specificity

(Sp=86.2%), i.e. in 86.2% of the cases positive test results make it possible to correctly diagnose a very high risk of disease development.

In children with hypertension this diagnostic test had higher sensitivity (Se=87.5%), while the specificity was the same (Sp=86.2%). At the same time, the integral assessment of the studied factor showed moderate validity (64.8% and 73.7%, respectively, for the comparison groups and the main one) and sufficiently high diagnostic efficiency (83.7 and 86.7, respectively, for the comparison groups and the basic one).

The CRP produced by the liver can directly damage the endothelium, indirectly activate other acute phase reactants, and accelerate the process of atherogenesis, atherothrombosis. CRP reduces the rate of fibrinolysis and promotes the synthesis of plasminogen activator inhibitor, stimulating the release of monocytic tissue factor, which reduces the concentration of NO and prostocycline and thus increases platelet adhesion. High level of CRP in healthy individuals is a risk factor for the development of CVD, and a potential diagnostic marker of ED [41, 87, 127]. In prospective observation the level of CRP in healthy subjects correlated with the level of systolic and pulse blood pressure. The CRP level is included in the Reynold scale for the assessment of the risk of developing cardiovascular problems, it has a predictive value in relation to CVD and mortality rate in both patients with cardiovascular pathology and in healthy examined patients [120, 126, 130]. In a number of modern reviews there is evidence that the variability of the increase in C-reactive protein as an indicator of systemic inflammation may have pathogenetic significance in the development of endothelial dysfunction in EAH cases [41, 53]. Recent studies have convincingly shown the important and independent role of the endothelium in the development of CVD. The endothelium is the first target organ that implements many links of the pathogenesis of various diseases, including EAH.

Thus, increase in blood pressure is associated with increase in CRPhs. In children with stable hypertension the level of CRPhs was significantly higher compared to the children with normal blood pressure values. In children with hypertension the definition of CRPhs has high sensitivity (Se=87.5%) and specificity (Sp=86.2%), but moderate validity (73.7%), and sufficiently high diagnostic efficacy (86.7).

Tumor necrosis factor - α (TNF-α) is expressed on the membrane of endotheliocytes and affects its functional properties. It also affects coagulation, disrupts lipid metabolism, stimulating the processes of atherogenesis. As an indicator of systemic inflammation TNF-α leads to decrease in myocardial contractility [66, 72, 79]. Gaiduk T.A. et al. (2018), when conducting variance analysis on the level of TNF-α between groups of children with hypertension, did

not reveal significant differences, but noted a tendency of TNF-α rise depending on the degree of hypertension stabilization[13].

Tumor necrosis factor alpha (TNF-α) secreted by macrophages is an indicator of systemic inflammation [113]. The counteraction to this process is the anti-inflammatory activity of IL-10 and its ability to influence the production of TNF-α by monocytes, in connection with which the concentration of these cytokines in blood serum of children with different levels of blood pressure and hypertension was determined.

Results of TNF-α and IL-10 in the examined groups are presented in Figure 2.

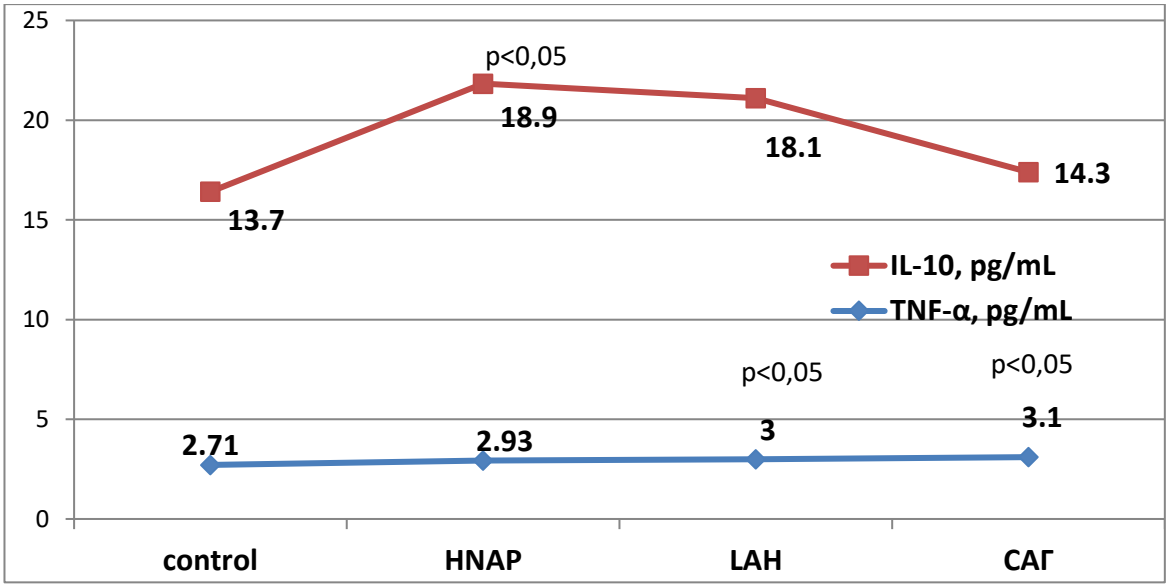

Figure 2. Average values of TNF-α and IL-10 in blood serum in the children of analyzed groups

According to the presented data the highest level of TNF-α was found in the group of children with stable hypertension ($p<0.05$) and the least high level in children with labile hypertension ($p<0.05$) compared with the values of the children from the control group. In children with HNAP 1.1 times increase in the level of TNF-α was noted in relation to the control with no statistical reliability.

The study of the concentration of anti-inflammatory cytokine IL-10 revealed a slight (4.4%) increase in its level in the children of the second basic group, whereas in children with HNAP these indicators were significantly higher relative to the control ($p<0.05$) and the values of the children with stable hypertension ($p<0.05$).

The average values of IL-10 in the children with labile hypertension were also high compared to the values of children with stable hypertension and the control group with no significant differences.

Inverse correlation was found between the level of IL-10 and TNF-α in the group of children with LAH ($r=-0.35$, $p<0.05$).

Thus, the regularities between the production of TNF-α and the activity of anti–inflammatory cytokine IL-10 have been established. At the same time, significantly high level of TNF-α ($p<0.05$) in the group of the children with SAH was associated with insufficient production of IL-10. But high concentration of IL-10 ($p<0.05$) in the children with HNAP was associated with a lower level of TNF-α ($r=-0.35$, $p<0.05$).

Hyperexpression of proinflammatory cytokines potentiates the expression of disorders in the blood rheology system, which is accompanied by increase in peripheral vascular resistance, contributes to the processes of remodeling of the vascular pool, violation of vascular tone, serving the trigger mechanism for the development and progression of hypertension [79]. At the same time, the level of TNF-α >2.84pg/ml causes the risk of EAH development in subsequent siblings 2.2 (RR=2.2) times higher than in case of its absence.

Anti-inflammatory cytokine IL-10 is one of the most sensitive markers of inflammation in CVD, which reduces the secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNF-α) and limits excessive immune response [29, 60, 76]. IL-10 reflects the reserve capabilities of the body. According to literature data, the amount of IL-10 in the blood of patients with CVD decreases [113]. Decrease in the plasma level of anti-inflammatory cytokines (IL-10) and increased amount of pro-inflammatory cytokines (TNF-α) and acute phase proteins (CRPhs) indicate a higher risk and unfavorable prognosis of CVD [71, 127].

Our clinical studies have shown that as blood pressure values increase, the level of proinflammatory cytokine TNF-α increases, with a statistically significant difference in relation to control in groups of the children with LAH and SAH. But the concentration of anti-inflammatory IL-10 does not decrease. Apparently, the physiological mechanisms of regulating the balance between pro- and anti-inflammatory cytokines are involved. A protective reaction develops: suppression of inflammatory processes, more pronounced in children with HNAP and no less pronounced in children with LAH. But with SAH, this reaction is less active; imbalance develops in the cytokine network with predominant activation of proinflammatory link (TNF-α). Perhaps this fact may play a role in the pathogenesis of SAH.

Inverse correlation was found between the level of CRPhs and blood pressure ($r=-0.37$, $p<0.05$ and $r=-0.58$, $p<0.001$, respectively, for SAP and DAP) in children with HNAP and the absence of such connections in the group of children with LAH. But in the group of the children with stable hypertension, there was a direct correlation of low strength between the level of CRPhs and DAP ($r=0.26$, $p>0.05$).

Only in the group of children with LAH there were significant correlations between CRPhs, TNF-α, and IL-10 ($r=0.48$, $p<0.05$, $r=0.42$, $p<0.05$, respectively) with a positive vector.

CHAPTER II. HEM DYNAMIC DETERMINANTS OF ENDOTHELIAL DYSFUNCTION AND THEIR ROLE IN THE DEVELOPMENT OF ESSENTIAL ARTERIAL HYPERTENSION IN CHILDREN

By the beginning of the XXI century a whole direction was created, which attracted the attention of clinicians to a new object of study – vascular endothelium. The importance of vascular endothelium is multifaceted and consists in maintaining homeostasis by regulating vascular tone (vasodilation and vasoconstriction processes); anatomical structure of vessels (synthesis and inhibition of proliferation factors); local inflammation (production of pro- and anti-inflammatory factors); hemostasis (synthesis and inhibition of fibrinolysis factors and platelet aggregation), etc. To date, at least 20 biologically active substances are known to be ensuring performance of corresponding functions of the endothelium [9, 22, 63].

According to the main functions of the endothelium the following forms of endothelial dysfunction can be distinguished: vasomotor, hemostatic, adhesive, and angiogenic. Vasomotor endothelial dysfunction is characterized by impaired synthesis of vasoactive substances. As a result, vasomotor activity of the endothelium decreases. Markers of endothelial vasomotor function disorders are blood levels of nitric oxide and endothelin -1, thromboxane A2, and prostocycline [60].

Recent studies have convincingly shown the important and independent role of the endothelium in the development of cardiovascular diseases (CVD). It is likely that many known risk factors for the development of CVD realize themselves precisely through changes in the properties of the vascular wall.

No less informative for assessing the vasomotor function of the endothelium in this regard are functional methods [67]. These methods include determination of endothelium-dependent vasodilation, vascular wall stiffness, and pulse wave propagation. In 2007 the European Association of Cardiologists, along with previously established criteria, namely left ventricular hypertrophy and increase in the thickness of the intima-media complex of the common carotid artery (TIM CCA), the indicator of endothelial dysfunction – increase in the rate of pulse wave propagation was included into the criteria for target organ lesions as a strong independent predictor of overall mortality in cardiovascular diseases [30].

The method of ultrasound examination of the features of post-occlusal changes in the diameter of the brachial artery developed by D. Celermajeru in 1992 has become more widespread. Temporary occlusion of the brachial artery is achieved by applying a cuff to the shoulder and pumping air, while the pressure in the cuff should

exceed systolic one. A high-resolution ultrasound sensor (7 MHz) detects change in the diameter of the brachial artery in response to increased blood flow after temporary occlusion (test with reactive hyperemia). The reliability, reproducibility and noninvasiveness of the method have identified it as one of the main ways to assess endothelial dysfunction [50, 70]. Currently, modern ultrasound Dopplerography, sphygmomonometric, pneumo-, photo- or electroplethysmographic methods are used to assess the function of the endothelium and remodeling processes. It is important to note that the peripheral endothelial function assessed by these methods correlates with endothelial dysfunction of the coronary arteries [99].

Currently, TIM CCA is a sonographic marker of early atherosclerotic vascular wall lesion and hemodynamic indicator of endothelial dysfunction. At the same time the numerical characteristics of the TIM CCA with its condition are evaluated, as well as the velocity indicators of blood flow in systole and diastole with the measurement of the diameter of CCA during these periods of the cardiac cycle [40, 57].

It has been established that thickening of IM CCA with high accuracy can predict the development of coronary diseases in adults who do not have clinical symptoms. During the initial phase of atherosclerosis an isolated change in the state of intima is noted – its echogenicity changes, differentiation into layers is disrupted, heterogeneity and unevenness of its surface appear. In this regard, it was proposed to use ultrasound examination of TIM CCA as a reliable non-invasive method for detecting atherosclerosis at the preclinical stage [47, 102]. However, this method has not yet been widely used in children.

In children, the diameter of the arteries increases with age, while changes in the vascular wall are not so obvious. Some authors note a slight increase in TIM CCA with age. In general, it can be noted that the measurement of TIM CCA in children and adolescents has excellent reproducibility. According to foreign researchers the average value of TIM CCA normally ranges from 0.31 to 0.61 mm. Such a spread of indicators of TIM CCA in children is explained by the fact that the authors could measure it at various places of CCA such as bifurcation area or distal parts of it. At the same time, the thickness of the intima in bifurcation area is usually greater than in the distal third of CCA. Besides that, technical characteristics of devices and measurement mode, age of children in the groups, apparently, could affect the values of the TIM CCA. It should be noted that most studies use data obtained during the examination of small control groups with 10-35 children [111, 134, 151].

TIM CCA correlates with the atherogenic lipid profile and the level of glycemia [21, 125]. When studying the relationship between CVD risk factors and TIM CCA association of thickening of IM CCA and severity of calcification of coronary arteries with cholesterol, low-density lipoproteins and systolic blood pressure was found. A. Wiegmanu et al. (2004) confirmed the influence of metabolic risk factors on TIM using the example of children and adolescents aged 8-18 years old from families with hereditary form of hypercholesterolemia [146].

Thus, thickening of IM CCA can be considered as an important predictor of cardiovascular risk and therefore should deserve special attention of pediatric cardiologists and therapists.

To study the features of the functional state of vascular endothelium duplex scanning of the right and common carotid arteries and brachial artery was performed in 97 children, in other words, the control group consisted of 25 children, the second group consisted of 25 children with high normal blood pressure, the third group 25 children with labile and the fourth 22 children with stable arterial hypertension.

Measurements of the diameter of the brachial artery (BA) and speed indicators of endothelial function, as well as TIM, were carried out on the device Sospare SSI-500, Mindray DR 6900, HD3 (Holland) with a 5.5-7.0 MHz linear sensor. Endothelium-dependent vasodilation (reactive hyperemia test) (EDV), endothelium-independent vasodilation (nitroglycerin test) (EIV) and velocity parameters (PA) in the examined groups were studied 30 seconds before the release of air from the cuff and 60, 90, 180 seconds after decompression. TIM CCA was measured 1 cm from the beginning of carotid bifurcation along the posterior wall of the common carotid artery (ultrasound border of intima – lumen - the place of internal measurement in mm; ultrasound border of media – adventitia - the place of internal measurement in mm). Measurements were carried out three times on each side, and the average 6 measurements in mm were calculated for the right and left carotid arteries and the total [70].

Parameters of TIM CCA: TIM CCAr, D CCAs, D CCAd, D CCA, VCCA .

Parameters of Duplex scanning of brachial artery: Dº, D 30, D 60, D 90, D 3', Dg, D max, EDV, D max, EIV, Vps or Max. LSS, Vpd or Max. LDS, RI, PI, MTABF, EIV%, EDV%, IVD.

Table 2

Mean parameters of the thickness of intima-media of common carotid artery in the examined children

Parameters	D CCAs, mm	D CCAd, mm	D CCA %	VCCA cm/sec	Measurement 1	Measurement 2	Measurement 3	Mean	Total mean
TIM of the right CCA, mm									-
1st group					0.53±0.029	0.52±0.028	0.54±0.03	0.53±0.025	
2nd group					0.58±0.031^,*	0.56±0.031^,*	0.55±0.025^*	0.56±0.03^*	
3rd group					0.64±0.034*	0.65±0.034*	0.65±0.031*	0.65±0.031*	
4th group					0.64±0.031*	0.66±0.032*	0.66±0.031*	0.66±0.031*	
TIM of the left CCA, mm									-
1st group					0.5±0.027	0.49±0.023	0.51±0.03	0.50±0.026	
2nd group					0.57±0.031^*	0.56±0.029^*	0.56±0.03^*	0.56±0.03^*	
3rd group					0.67±0.031*	0.66±0.044*	0.65±0.04*	0.66±0.04*	
4th group					0.68±0.033*	0.67±0.05*	0.66±0.05*	0.67±0.05*	
Total mean values, mm					-	-	-	-	
1st group	0.59±0.014	0.54±0.013	15.2±0.73	84.3±0.88					0.66±0.023
2nd group	0.57±0.012^, *	0.51±0.011^, *	13.5±0.56^,*	85.9±0.91					0.56±0.030^, *
3rd group	0.55±0.005	0.48±0.005*	10.6±0.30*	87.1±1.01					0.52±0.030*
4th group	0.55±0.006	0.48±0.005*	10.7±0.37*	87.9±1.06					0.51±0.033*
Note: * – p< 0.05 - 0.001, reliability of difference compared to the control, ^ - p< 0.001 reliability of difference compared to the 3rd group.									

Color duplex scanning of the extracranial sections of the brachiocephalic arteries in children of the basic groups revealed significant increase in the thickness of intima-media complex of the right common carotid artery to 0.66±0.03 mm at the second measurement, relative to the control and 2 groups (0.53±0.029 mm; p<0.001, 0.56±0.03 mm, p<0.001, respectively) (table. 2) The average values of the TIM of the right CCA of the basic groups (0.65±0.03 mm) also significantly exceeded the indicators of the children of the 1 (0.53±0.025, p<0.001) and 2 (0.56±0.03 mm, p<0.001) groups. A similar trend of increasing TIM is also observed on the left CCA with reliable distinctive features. Statistically significant thickening of TIM was found in the children of the main group by the value of the total average of 6 measurements against the control and comparative group (0.51±0.023 mm; p<0.001, p<0.001, 0.56±0.030; p<0.001, p<0.001, respectively).

The smallest index of the CCA diameter in systole was in children with hypertension, decreasing by 7.3%, and in diastole by 12.5%, similar to the indicator in the control with significant difference (p<0.001, p<0.001, respectively). Significant decrease in these indicators is also observed in children with HNAP in relation to the control (p<0.001, p<0.001, respectively).

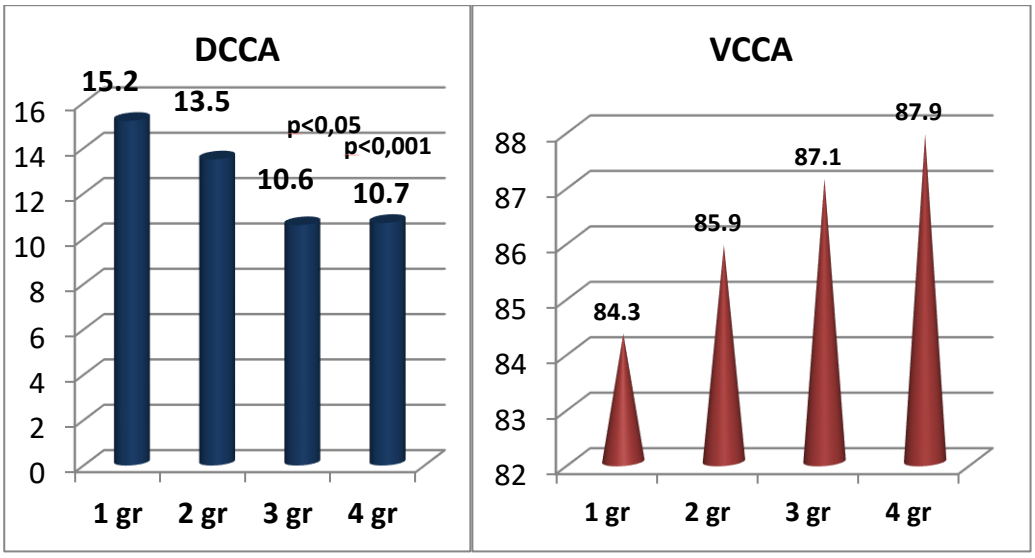

Figure 3. Comparative analysis of the values of the diameter (D) of CCA (%) and systolic blood flow velocity (V) in CCA (cm/sec)

A comparative analysis of the diameter (D) of CCA in % (Fig. 3) revealed significant decrease in the diameter of the common carotid artery during the cardiac cycle in the children with hypertension in relation to groups 1 and 2 (p<0.001, p<0.001, respectively). In children with high normal blood pressure, these values were significant, but with minimal difference (p<0.05).

Systolic blood flow rate also tends to increase by 2.1% in the children with hypertension and 0.7% in children with HNAP compared to control.

It is known that the process of vascular remodeling includes stages of functional and morphological changes that lead to violation of the main vascular functions, i.e. increase in the carotid artery TIM and decrease in the elasticity of the artery. Structural changes in the middle shell of the carotid artery (media) are directly dependent on increase in the level of endothelin in blood plasma, which confirms the role of ED in the development and progression of vascular remodeling processes. The study of TIM makes it possible to assess the risk of developing cardiovascular diseases.

According to the results of our study, in the children with high blood pressure (group 2) the average TIM CCA exceeded the normal limits by 9.8% ($p<0.001$), and in the children with hypertension there was significant increase in this value ($p<0.001$) both in relation to the control and the comparison group. This indicates that these markers of impaired vasomotor function and TIM CCA manifest much earlier in the development of hypertension compared to other parameters.

Thus, ultrasound examination of the common carotid artery is convenient and reliable way of early detection of arterial lesions at target organs in children and adolescents with risk of cardiovascular diseases development. The study showed that, compared with school-age children with normal age-related blood pressure children with high blood pressure and hypertension have non-physiological changes in the vascular wall, manifested by higher values of TIM CCA.

In the present study, endothelium dependent vasodilation (EDV) of BA was evaluated during a test with reactive hyperemia proposed by Celermajer et al. (1992) modified by T.V. Balakhonova (1998). After restoration of the initial diameter of the artery, endothelium-independent vasodilation (EIV) was evaluated by measuring the diameter of the BA after sublingual administration of 500 mcg of nitroglycerin. The reaction to increased blood flow was calculated as the difference in diameters with the background reactive hyperemia and the initial one.

It was found that at rest the average diameter of the BA in children with hypertension was 2.45 ± 0.19 mm, which is slightly less than in children of groups 1 and 2 (2.56±0.15 and 2.53± 0.13 mm, respectively) (Table 3).

Analysis of the dynamics of the diameter of the BA and the linear velocity of blood flow in a sample with EDV in the analyzed groups showed that the most reliable values of these parameters are observed at the point of 30 and 60 seconds after decompression.

Besides that, we noted increase of BA diameter to 2.86±0.19 mm in the children with AH, being 1.2 and 1.1 times less than in the 1st and 2nd groups ($p<0.05$, $p<0.05$, respectively). The highest growth of the BA diameter was noted in the children of the 1st group with 26.7±2.13% compared to the children with AH (15.6±1.41%, $p<0.001$).

Table 3

Mean values of brachial artery dilation with blood flow linear velocity in the examined children

Parameters	1st group control	2nd group HNAP	3rd group LAH	4th group SAH
D°	2.56±0.15	2.53±0.16	2.45±0.2	2.45±0.11
D 30	3.02±0.16	2.91±0.17	2.86±0.2*	2.87±0.2*
D 60	3.18±0.20	3.01±0.20	2.86±0.1*	2.86±0.2*
D 90	2.86±0.2	2.82±0.2	2.82±0.2	2.82±0.2
D 3'	2.59±0.17	2.57±0.18	2.55±0.2	2.55±0.2
Dg	26.7±2.24	24.7±2.1	15.6±1.5	15.6±1.5
D max, EDV	3.53±0.082	3.49±0.082	3.17±0.070***	3.18±0.070***
D max, EIV	3.60±0.084	3.58±0.084	3.24±0.072**	3.28±0.072***
Vps or Max. LSS	85.99±1.13	82.83 ±1.31	79.12±1.24*	79.15±1.24*
Vpd or Max. LDS	2.68±0.90	2.4±1.10	- 1.8±1.14*	- 1.8±1.16*
RI	0.96±0.092	1.0±0.092***^^^	1.14±0.02***	1.14±0.01***
PI	1.84±0.12	1.84±0.10	1.88±0.11	1.89±0.12
MTABF	43.33±0.15	39.50±3.57	35.47±3.5	35.51±3.57
EDV%	16.01±0.14	15.21±0.17***^^^	12.31±0.13***	12.02±0.13***
EIV%	24.1±0.31	20.1±0.41***^	18.89±0.40***	18.78±0.32***
IVD	1.50±0.01	1.52±0.01***^^^	1.57±0.018***	1.58±0.017***

Note: * – p<0.05, ** – p<0.01, *** – p<0.001, reliability of difference compared to the control, ^^^ - p<0.001, ^ - p<0.05, reliability of difference compared to the 3rd and 4th groups.

The initial maximum blood flow velocity averaged 60.3±6.0 and 55.34±5.3cm/sec in children of the 1st and main groups, respectively (p>0.05). The dynamics of blood flow velocity in response to temporary vessel occlusion also did not differ statistically between these groups (p>0.05).

The increase in BA diameter in the 3rd and 4th main groups was significantly less than in the 1st and 2nd groups (p<0.001, p<0.001, respectively, for groups 3 and 4). A similar trend can be traced with EDV BA with significant decrease in BA dilation in two main groups (p<0.001, p<0.001, respectively) (Fig. 4.).

The index of Purcelo resistivity significantly differed in the children with hypertension with the same orientation, the values of IR increased with the rise in blood pressure and were maximal in children of the 4th, 3rd and 2nd groups (p<0.001, p<0.001, p<0.001, respectively). Changes in the indicators of the Gosling pulsativeness index had similar trend only without significant differences.

Thus, vascular endothelial dysfunction was more pronounced in the children with hypertension. But, the condition of high normal blood pressure was also accompanied by violation of EDV.

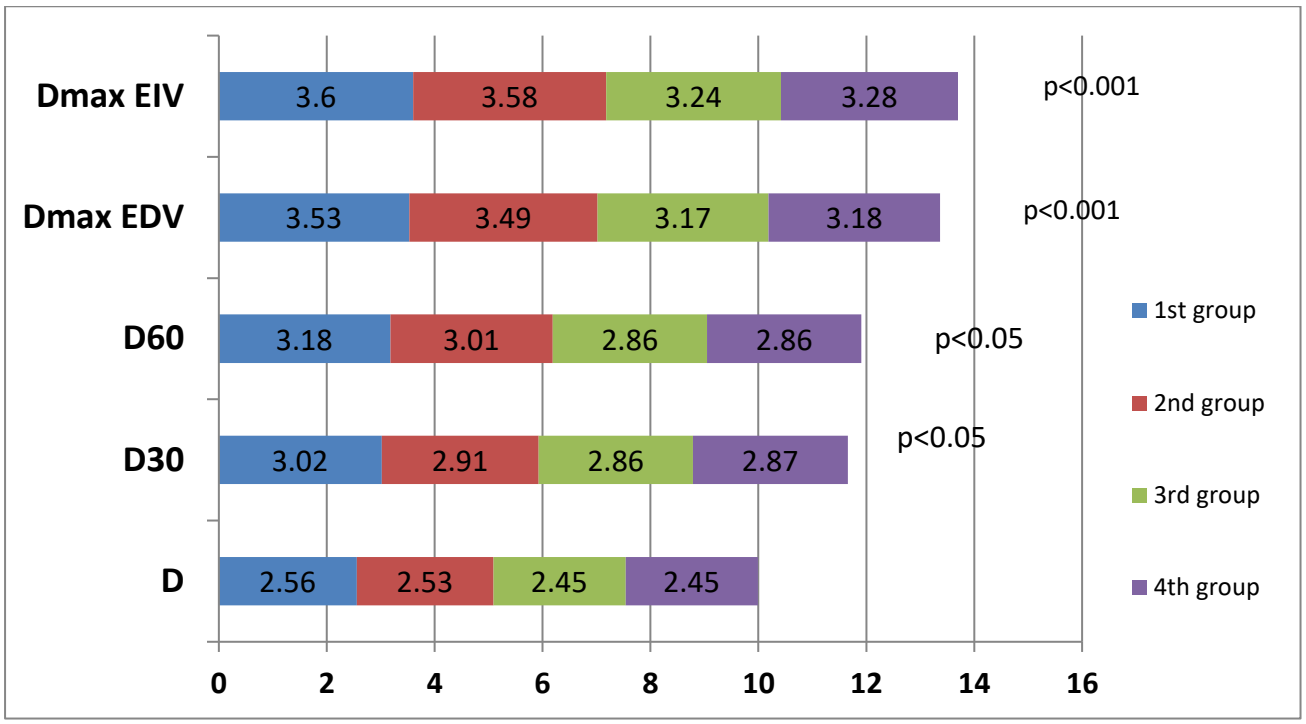

Figure 4. Mean values of brachial artery dilation in the examined children

Linear blood flow rates decreased in the children with high blood pressure and hypertension with significant difference only for the main groups ($p<0.05$), which indicates violation of the functioning of blood vessels. The values of IR and PI increased with the rise in blood pressure and were maximal in the children with hypertension. Identical picture emerges with respect to the values of IVD (the vasodilation index) with significant difference in the indicators of the 2nd, 3rd, and 4th groups of children compared to the control ($p<0.001$, $p<0.001$, $p<0.001$, respectively).

CHAPTER III. VITAMIN D SUPPLY AND ENDOTHELIUM-DEPENDENT MARKERS OF ARTERIAL HYPERTENSION IN CHILDREN

To date it has been irrefutably proven that vitamin D, as a hormone, with the formation of its "hormone-like axis: calcidiol -calcitriol - VDR (vitamin D receptor)" is closely interrelated not only with parathyroid hormone and calcitonin, but also with the biological effects of insulin, estrogens, neurotrophic factors, and cytokines [19, 42, 81 103]. In this regard, it is possible to simulate the consequences of inadequate vitamin D levels in the human body with the help of problems ranging from child growth retardation to a wide range of chronic diseases that take lives of hundreds of millions of adults [82, 96, 115, 131]. Evidence of the positive effects of vitamin D stimulated the development of nationwide recommendations to eliminate its deficiency in Poland (2009, 2013) [122], Hungary (2012) [138], Germany, Austria and Switzerland (2012) [153,], and the Russian Federation (2018) [107]. The Institute of Medicine of the National Academy of the USA together with the Society of Endocrinologists also developed their own principles on vitamin D (2011) [108]. In 2012 the European Food Safety Authority issued revised levels (upper limits) of vitamin D for all relevant populations. Calcidiol level 25(OH)D in serum is accepted as a standard biomarker of the body's vitamin D supply. This metabolite is quite stable (half-life 2-3 weeks), it reflects the intensity of vitamin D synthesis in the skin and intake with food [90, 104, 106].

In numerous clinical studies examining level of 25(OH)D in the context of its relationship with the state of human health and the risk of developing diseases, adequate levels of 25 (OH)D are shown in the range from 30 to 50 ng/ml (75-125 nmol/L) and the required minimum concentration (>20 ng/ml or >50 nmol/l) for the normal existence of the organism [83, 93, 105].

The data of the world literature indicate the problem of vitamin D deficiency, which is acquiring the scale of epidemic and coincides with the increase in the prevalence of non-communicable diseases (NCDs) [97, 133]. Population studies among children also indicate high prevalence of hypovitaminosis D [68, 77, 142]. According to the results of a study conducted in the United Arab Emirates, despite the presence of sufficient insolation, a higher frequency of vitamin D deficiency was found in children from 8 to 14 years old compared with children 2-7 years old [194]. In this connection, national recommendations were developed [101].

Prospective researches of D.I. Akhmedova et al. (2019) on the study of the level of 25-hydroxyvitamin D in 239 children aged 2-3 years old living in various regions of the Republic of Uzbekistan during the period of maximum insolation also revealed deficiency of vitamin D in 18.4% and insufficient lavel in 63.6% of them [8].

It is known that up to 80% of vitamin D can be synthesized in the skin with sufficient insolation of the exposed skin surface by ultraviolet radiation with wavelength of 280-315 nm. But the synthesis of vitamin D depends on the angle of the sun's rays, i.e. geographical latitude, time of year and time of day. Besides that, prolonged stay indoors, swarthy skin color, intense tan, insufficient physical activity, smog, high cloud cover reduce vitamin D production. The geographical location of our country above 350 north latitude is one of the reasons for the low status of vitamin D [11, 139]. The results obtained indicate that vitamin D coming from food and synthesis in the skin does not provide an adequate level in the body to maintain health. In this connection, it is relevant to develop national programs for the prevention and treatment of insufficient and deficient levels of vitamin D in children and adolescents.

The presence of a link between the level of 25 (OH)D in blood serum and blood pressure indicators have been established in various studies [25, 45, 148]. A meta-analysis of 11 placebos–controlled studies (5,660 patients aged from 6 months to 75 years old) confirmed the protective effect of taking vitamin D against respiratory tract infections (influenza, pneumonia, acute respiratory diseases) [80, 152]. Higher levels of vitamin D in blood serum correlated with improved lung function in patients with cystic fibrosis [49], with 43% reduction in the risk of type 2 diabetes and metabolic syndrome (according to the results of a meta-analysis of 28 studies in 99,745 patients) [122].

Meta-analysis of 7 cohort studies involving more than 43 thousand people established a link between low level of 25(OH)D and high prevalence of hypertension for 7-8 years [145]. S. Pilz et al. in a randomized controlled trial recorded that taking vitamin D contributed to decrease in SAP by 2-6 mmHg [121]. According to the results of a large-scale NHANES (National Health and Nutrition Examination Survey 2001-2004) study in the USA, 61% of adolescents aged 12-19 (n=4666) had insufficient vitamin D levels (15-29 ng/ml) and 9% had its deficiency (<15 ng/ml). These vitamin levels were associated with high SAP and low HDL levels. A Spanish study of 149 children aged 8-13 years old demonstrated relationship between high levels of TH and low levels of vitamin D [128].

Low vitamin D levels are associated with ventricular hypertrophy, ED, and activation of renin-angiotensin system (RAS). It has been proven that in vitro the active form of the vitamin suppresses RAS, while the renin gene in the promoter region has vitamin D-a sensitive element through which the vitamin has a direct regulatory effect on its transcription and renin production [17].

In the research of L.V. Yakovleva et al. (2017) it was found that there was inverse reliable correlation between the levels of vitamin and renin in blood plasma of adolescents with hypertension, while the level of vitamin D deficiency and renin concentration did not depend on the degree of hypertension [75].

Vitamin D deficiency directly affects the muscle wall of blood vessels, leading to increased vascular resistance, increase in the thickness of intima-media complex (TIM) [18, 107, 109]. Vitamin D plays a role in the transport of calcium into vascular smooth muscle cells, inhibits the release of cytokines from lymphocytes, and affects inflammation and lipid metabolism [58, 112, 117]. Such a multifaceted role of vitamin D is due to its effect on the immune system. The data available to date indicate that the immunomodulatory effect of the vitamin is realized by suppressing the synthesis of pro-inflammatory cytokines (IL-1, IL-2, IL-6, TNF-α, IL-8, IL-12) and stimulating the production of anti-inflammatory ones (IL-4, IL-5, IL-10, TNF-B1), inhibiting the development of type 1 T-helpers, increasing type 2 T-helpers and restoring regulatory T-lymphocytes [54, 58, 129].

The relationship between the body's vitamin D supply and endothelium-dependent risk factors of EAH development in children has not been found according to available literature data, which requires further in-depth research.

3.1. Vitamin D (25 (OH)D_3 active metabolite) supply in school age children with normal, HNAP, and EAH

The results of systematic reviews and meta-analyses conducted in the adult population indicate the role of vitamin D deficiency in the occurrence and progression of cardiovascular diseases, but such studies are rare in children. Serum content of vitamin D - 25 metabolite(OH)D is the main circulating form reflecting both skin synthesis and assimilation with food [29, 64]. In this connection, in order to solve this task, we conducted studies of 25 (OH)D level in the blood serum of 132 schoolchildren. Interpretation of the level of 25(OH)D in the blood serum of the children was carried out in accordance with the National Program of the Russian Federation on the provision of vitamin D [64].

Level of 25(OH)D in blood serum was determined using commercial kits "DIAsource" (Belgium) on the analyzer "Stat Fax 2100" (Israel) according to the methodology of quantitative enzyme solid-phase analysis ELISA.

The level of vitamin D supply in schoolchildren in Tashkent is shown in figures 5 and 6.

The presented data showed that only 18 (13.6±2.9%) children had optimal vitamin D level (the average level of 25(OH)D_3 was 31.1±0.39ng/ml), 37 (28.0±3.9%, $p<0.05$) had insufficient content (23.2±0.61ng/ml, $p<0.001$), 43 (32.6±4.1%, $p<0.05$) children were diagnosed with vitamin D deficiency (14.9±0.48 ng/ml, $p<0.001$) and 34 (25.8±3.8%, $p<0.05$) suffered severe deficiency (8.19±0.23 ng/ml, $p<0.001$). The

average vitamin D content in 132 children was 17.7±0.89 ng/ml, which indicates deficient vitamin D level.

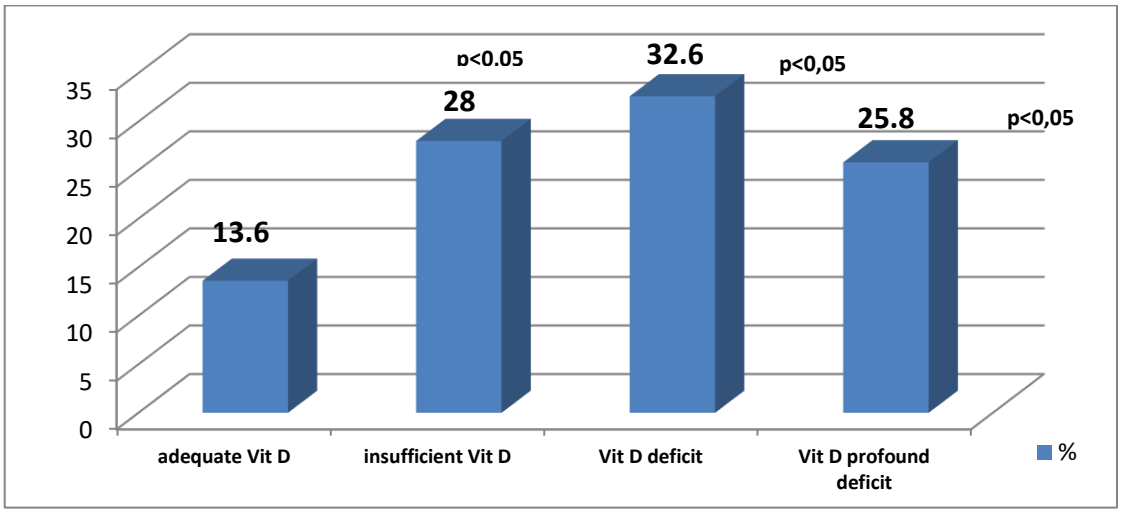

Figure 5. Vitamin D supply in schoolchildren in Tashkent

The results obtained coincide with the literature data. Studies of the level of 25(OH)D_3 by A.A. Kozlovsky (2017) in school-age children (7-18 years old) in Gomel showed reduced average content of the vitamin D metabolite with 22.17±1.39 ng/ml. [31].

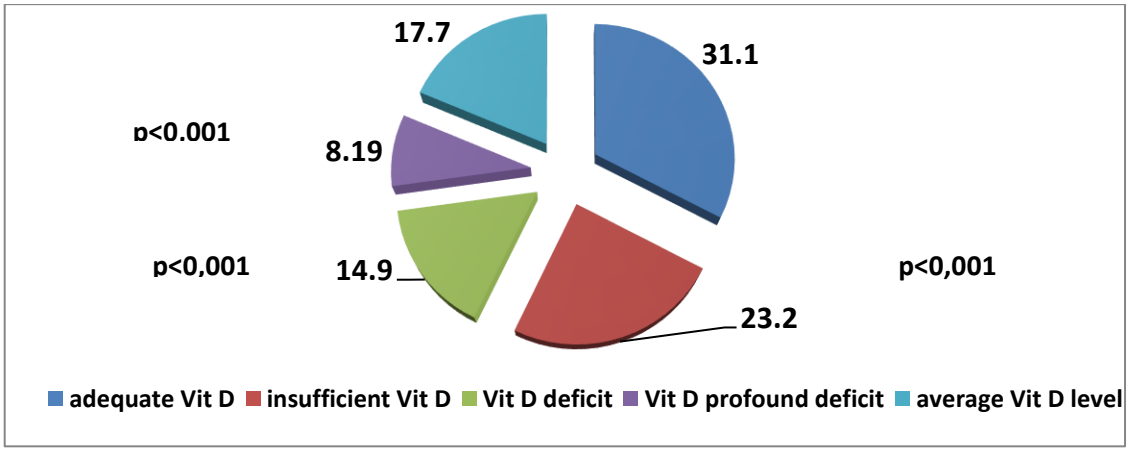

Figure 6. Mean values of vitamin D supply in schoolchildren in Tashkent (ng/mL)

A multicenter study "Rodnichok-1" conducted in Russia found vitamin D deficiency in 42% of children from birth to 3 years old [20, 64]. I.N. Zakharova's private study conducted in February 2011, which included 100 teenage girls aged 11-17, on the basis of the Moscow Cadet Corps FGCOU, revealed hypovitaminosis D in almost half of the participants [64]. The following work was carried out with

teenagers in Moscow, in which year–round vitamin D deficiency was noted and the most profound deficiency at the level of vitamin deficiency was established in May. Normalization of vitamin D status in adolescents did not occur during the summer months.

The frequency of occurrence of different levels of vitamin D in children, depending on blood pressure parameters is shown in Table 4.

Table 4.

Prevalence of various levels of vitamin D supply in schoolchildren in Tashkent dependent on AP level (abs/%, ng/mL)

25(OH)D	Control group n=43		HNAP n=42		LAH n=25		SAH n=22	
	abs	%	abs	%	abs	%	abs	%
Adequate level of vitamin D >30 ng/mL	20	46.5±7.6	-	-	-	-	-	-
Vitamin D insufficiency 21-30 ng/mL	21	48.8±7.6	17	40.5±7.6	3	12.0±6.5*	1	4.5±4.4*
Vitamin D deficit <20 ng/mL	2	4.7±3.2	19	45.2±7.7*	11	44.0±9.9*	10	45.5±10.6*
Vitamin D profound deficit <10 ng/mL	-	-	6	14.3±5.4	11	44.0±9.9^	11	50.0±10.6^
Average level of vitamin D, ng/mL	27.4±0.92		16.3±1.2***		12.35±1.1***		11.8±1.1***	

Note: reliability of difference for ***- $p<0.001$, compared to the control; ^ - $p<0.01$ compared to the group with HNAP.

According to the table, it can be seen that the prevalence of vitamin D deficiency in children of the basic groups was significantly lower than in the control group ($p<0.001$ and $p<0.001$, respectively, in the 1st and 2nd main groups). The same trend, but with inverse vector, was noted with respect to the prevalence of vitamin D deficiency starting from the comparison group with respect to the control ($p<0.01$, $p<0.01$ and $p<0.01$, respectively, in the comparison group, in the 1st and 2nd basic groups). Pronounced deficiency or beriberi was diagnosed only in children with high blood pressure and hypertension, with significantly high prevalence rate in the main groups relative to the comparison group ($p<0.01$ and $p<0.01$, respectively, in the 1st and 2nd basic groups).

Adequate vitamin D content was observed only in the children of the control group. At the same time the average concentration of 25(OH)D in children of this group was assessed as insufficient one (Fig. 7).

Reliably low values of 25(OH)D in children in the comparison groups ($p<0.001$) and the main groups ($p<0.001$ and $p<0.001$, respectively, in the 1st and 2nd groups) in relation to the control had tendency for deficiency.

Thus, the study and assessment of the supply of vitamin D in schoolchildren showed that only 13.4±3.8% of the children had optimal level of vitamin D with average level of 25(OH)D 31.1±0.39ng/ml. We registered significantly high frequency of insufficient content (28.0±4.9%, $p<0.05$), vitamin D deficiency (32.9±5.2%, $p<0.05$) and profound vitamin D deficiency (25.6±4.8%, $p<0.05$). Deficiency level was established (17.7 ± 0.89 ng/ml) according to the average vitamin D amount in children

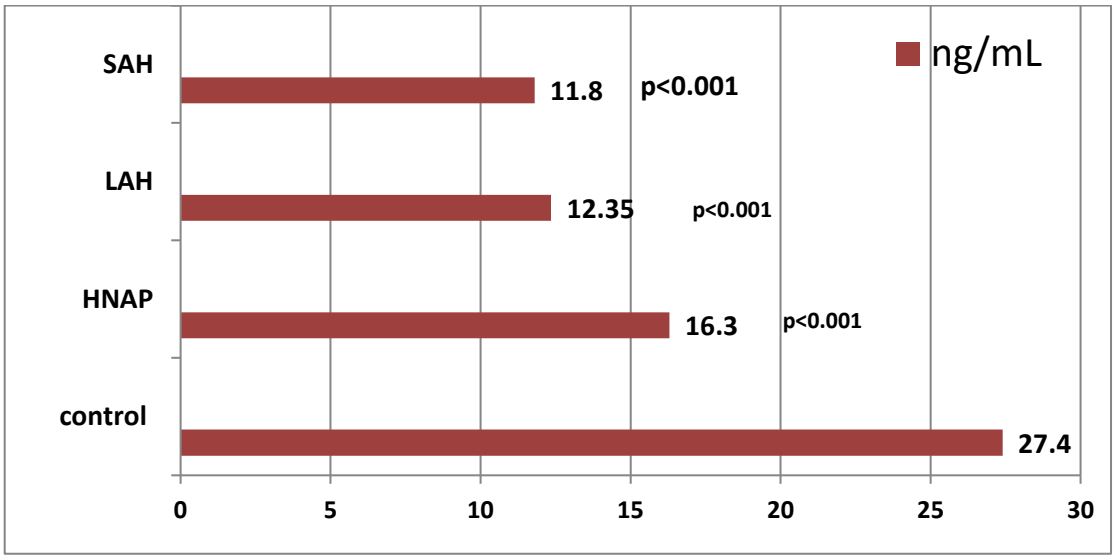

Figure 7. Average level of vitamin D in the studied groups, ng/mL

Analysis of vitamin D supply in schoolchildren depending on blood pressure indicators established significantly high prevalence of vitamin D deficiency in the children with high blood pressure ($p<0.001$) and hypertension ($p<0.001$) in relation to children with normal blood pressure. The diagnostic test of vitamin D deficiency for the comparison group and the 1st basic group had 90% (Se=0.90= 90%) sensitivity, 68% (Sp=0.68= 68%) specificity and relative risk RR=11.25, and for the 2nd group, 89% (Se=0.89= 89%) and 70% (Sp=0.70=70%) sensitivity and specificity, respectively, and RR=10.0.

Profound deficiency was noted in the children with HNAP and hypertension with significantly high prevalence in the basic groups with respect to the comparison group $p<0.01$ and $p<0.01$, respectively, in the 1st (Se=0.75, Sp=0.61, RR=3.0) and in the 2nd (Se=0.75, Sp=0.65, RR=3.3,) ones.

Comparative analysis of the average parameters of serum calcium levels in children with different blood pressure levels is shown in Figure 8.

The calcium level was determined in blood serum using biochemical analyzer "Minray BS-200" (China) using commercial kits "Human" (Germany).

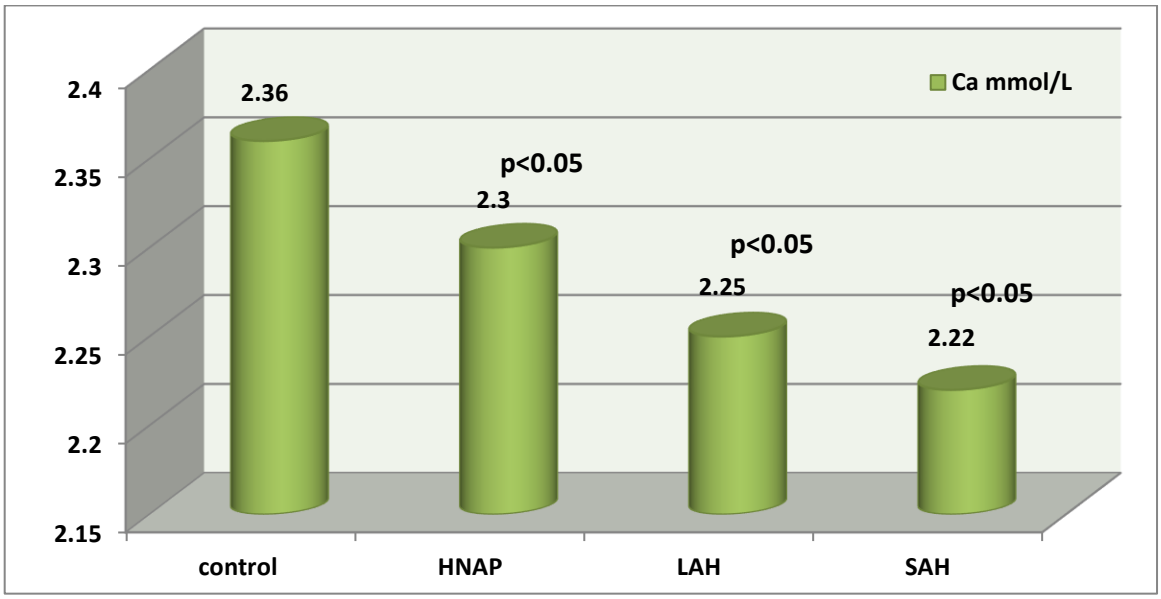

Figure 8. Average values of Ca in blood serum of the children in the studied groups

The data in the figure show that the compared parameters of calcium level did not go beyond the normative range. But the average values of serum calcium concentrations in the children with high blood pressure ($p<0.05$), with stable hypertension ($p<0.05$) and with labile hypertension ($p<0.05$) were significantly low compared with healthy children.

3.2. Peculiarities of endothelin 1-21 distribution in schoolchildren with normal, high normal arterial pressure and essential arterial hypertension

Endothelin-1-21 (E-1) is the most powerful vasoconstrictor factor, the main activators of the synthesis of which are hypoxia and local ischemia [95]. E-1 enhances cytokine production and thereby initiates the inflammatory process [59].

As a rule, to realize its function E-1 binds to two types of receptors: type A localized on vascular MMC, and type B localized on endothelial and MMC, and activation of these receptors causes vasoconstrictor and mutagenic effect.

Despite the importance of the problem ED remains one of the most studied factors of cardiovascular problems and at the same time the least studied sections of experimental and clinical medicine. The question of what place E-1 occupies in the pathogenesis of EAH in children and adolescents remains debatable which determines the relevance of further research in this area.

Concentration of endothelin-1-21 was determined in blood serum using commercial BIOMEDICA kits (Austria) on the analyzer "Stat Fax 2100" (Israel) according to the methodology of quantitative enzyme solid-phase analysis ELISA.

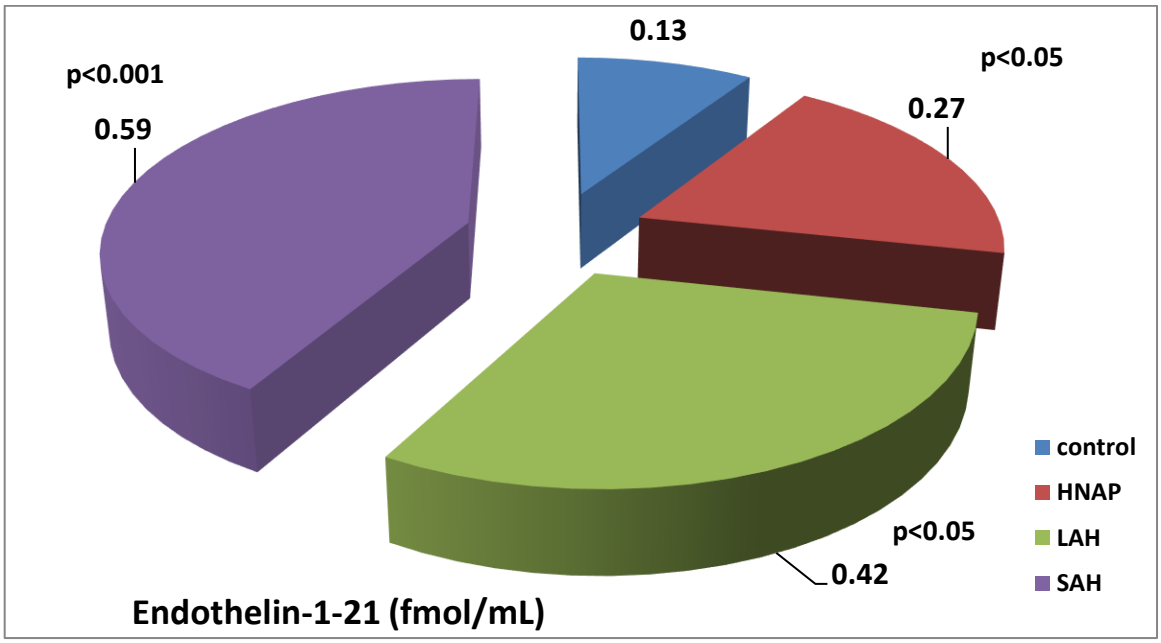

Figure 9. Comparative analysis of endothelin 1-21 level in the children of the studied groups

Our studies of the level of endothelium-dependent vasoconstrictor factor endothelin – 1-21 (E-1) showed increase in its serum values in the children with high normal blood pressure and hypertension (Figure 9).

According to the data presented, it was found that in the children of the control group the level of E-1 did not exceed the reference values (<0.26 fmol/ml), whereas in the children with HNAP (0.27±0.05 fmol/ml, p<0.05), LAH (0.42±0.1 fmol/ml, p<0.05) and SAH (0.59±0.1 fmol/ml, p<0.001) this level was significantly higher than in the control (0.13 ±0.02 fmol/ml).

The prevalence of high levels of endothelin -1-21 depending on the blood pressure in the analyzed groups is shown in Table 5.

According to the table, it can be seen that the frequency of E-1-21 level indicators >0.26 and >1.0 fmol/ml in children with SAH was 2.4 and 1.6 times higher (OR=2.4; RR=1.5 and OR=1.6; RR=1.5, respectively) than in children with LAH. But in the children with HNAP the frequency of E-1-21 levels >0.26 fmol/ml was identical to the group of children with SAH (60.0±10.9%, versus 61.1±11.5%, respectively), which indicated early signs of ED in the children with high normal blood pressure. This test has 100% sensitivity and 0% specificity in the early diagnosis of ED.

Table 5.

Prevalence of high values of endothelin -1-21 dependent on AP (abs/%, fmol/mL)

Endothelin-1-21, fmol/mL	I group Normal AP (control) n=20		II group HNAP (comparison) n=20		III group LAH (1st basic) n=20		IVgroup SAH (2nd basic) n=18	
	abs	%	abs	%	abs	%	abs	%
<0.26	24	100.0	8	40.0±10.9	9	45.0±11.1	3	16.7±8.8
>0.26; <1.0	-	-	12	60.0±10.9	8	40.0±10.9	11	61.1±11.5
>1.0	-	-	-	-	3	15.0±7.9	4	22.2±9.8

Our results are compatible with the literature data. In the studies of Aflyatumova G.N. et al. (2017) the level of E-1-21 in adolescents with a stable form of EAH was significantly higher than in the labile variant (1.67 ± 0.12 vs. 1.14 ± 0.13 fmol/ml, respectively) [8]. Also, the indicators of the level of E-1-21 in children with labile hypertension were significantly higher than in the control (1.38 ± 0.13 vs. 0.8 ± 0.08 fmol/ml, respectively; $p < 0.001$).

It was found that physiological concentrations of E-1-21 affect endothelial receptors, causing the release of relaxation factors, and higher concentrations of it activate receptors on smooth muscle cells, causing their persistent vasoconstriction and proliferation of media. Thus, two opposite vascular reactions (dilation and constriction) controlled by the feedback mechanism are regulated by the same factor [14].

The obtained results serve the basis for the development of effective non-drug and drug therapy based on E-1-21 receptor antagonists, which is especially important for children and adolescents with high blood pressure and hypertension, as a way to prevent EAH and its complications in the adult period.

3.3. Diagnostic and prognostic significance of vitamin D and endothelin 1-21 in the development of arterial hypertension in children with the assessment of endothelial dysfunction markers

In our work in order to identify causal relationships between the factors of vitamin D availability and serum levels of calcium, endothelin-1-21 and the

parameters of physical development in cases of essential hypertension in children, depending on the blood pressure level, mathematical correlation analysis was carried out between the above values (Table 6).

Table 6

Parameters of correlations between vitamin D and Ca, endothelin-1-21 in blood serum, parameters of physical development, systolic and diastolic arterial pressure, inflammation factors and hemodynamic values in the examined groups

25(OH)D	Control group n=20		HNAP n=20		LAH n=20		SAH n=18	
	r	p	r	p	r	p	r	p
Ca	0.41	-	0.66	<0.01	0.34	-	0.03	-
Endothelin	-0.05	-	-0.80	<0.001	-0.66	<0.01	-0.79	<0.001
Height	0.45	<0.05	0.36	-	0.38	-	0.35	-
Weight	0.62	<0.01	0.17	-	0.44	<0.05	0.23	-
BMI	0.47	<0.05	0.06	-	0.31	-	0.05	-
SAP	0.40	-	0.25	-	-0.47	<0.05	-0.65	<0.01
DAP	0.48	<0.05	0.63	<0.01	-0.64	<0.01	-0.50	<0.05
CRPhs	-0.02	-	-0.62	<0.01	-0.58	<0.05	-0.52	<0.05
TNF-a	-0.05	-	-0.51	<0.05	-0.23		-0.33	-
IL-10	0.25	-	0.67	<0.01	0.44	<0.05	0.38	-
Dg_{PA}	0.40	-	0.36	-	0.47	<0.05	0.50	<0.05
TIM CCA	0.45	<0.05	0.23	-	0.51	<0.05	0.45	<0.05

According to the table, it can be seen that strong negative correlations were established between the level of vitamin D and endothelin -1-21 in the comparison groups (r=-0.80, p<0.001) and the two main groups (r=-0.66, p<0.01 and r=-0.79, p<0.001, respectively, in the groups of children with LAH and SAH), which indicates

interdependence between vitamin D deficiency and the severity of endothelial dysfunction.

The results obtained by us are compatible with the literature data. Kodentsova V.M. et al. (2017) established association between the insufficient supply of vitamin D in the body and occurrence of three mutually influencing processes: oxidative stress, inflammation, and endothelial dysfunction [29].

The level of vitamin D provision had a positive correlation of average strength with the parameters of physical development (with values of height: $r=0.45$, $p<0.05$; weight: $r=0.62$, $p<0.01$; BMI: $r=0.47$, $p<0.05$) in children of the control group. But these interdependencies lost their validity and reliability in the groups of children with high blood pressure and hypertension.

Between blood pressure parameters and level of 25(OH)D we observed multidirectional correlations, where the relationship between high blood pressure values and low vitamin D levels in children of the basic groups is logically traced.

In the control group (Fig. 10) of children direct correlation of weak strength was noted between blood pressure indicators ($r=0.40$, $p>0.05$ and $r=0.48$, $p<0.05$, respectively, for SAP and DAP).

A rather specific dynamics of relationships is monitored in relation to the values of SAP and DAP in the groups of children with HNAP, LAH, and SAH. In the group of children with HNAP there was direct dependence of the level of diastolic blood pressure on the degree of vitamin D availability ($r=0.63$, $p<0.01$). A change in the polarity of the connections was noted in the relationship between vitamin D levels and the values of SAP and DAP in the main groups: the priority effect vitamin D availability had on the level of DAP ($r=-0.64$, $p<0.01$) in the group of children with LAH, but in the group of children with SAH this effect was directed to the parameters of systolic blood pressure ($r=-0.6$, $p<0.01$).

A single reliable correlation was established between the levels of vitamin D and Ca ($r=0.66$, $p<0.01$) in the group of children with HNAP. In the control ($r=0.41$, $p>0.05$) and main ($r=0.34$, $p>0.05$ and $r=0.03$, $p>0.1$) groups of children the abovementioned similar reliable correlation was absent.

The results of the mathematical analysis of paired correlations between the level of endothelin-1-21 and the values of Ca in blood serum, parameters of systolic and diastolic blood pressure in the analyzed groups are shown in Figure 10.

The only reliable correlation between the level of endothelin-1-21 and the values of Ca ($r=-0.68$, $p<0.01$) in blood serum with a negative vector was revealed in the second main group of children.

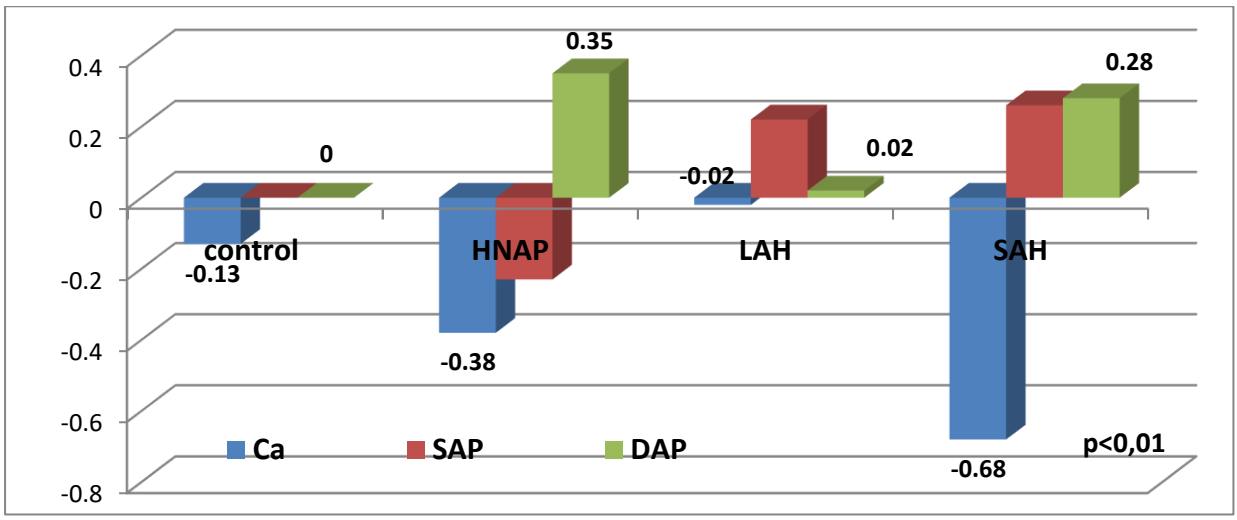

Figure 10. Structure of correlations between endothelin-1-21 and Ca in blood serum, systolic and diastolic arterial blood pressure in the studied groups

Thus, in the mechanism of EAH development in children there is interdependence between vitamin D deficiency and the severity of endothelial dysfunction in terms of endothelin -1-21 ($r=-0.79$, $p<0.001$), as well as the priority effect of vitamin D availability on the level of DAP ($r=-0.64$, $p<0.01$) in the group of children with LAH, but in the group of children with SAH, this effect was directed at the parameters of systolic blood pressure ($r=-0.6$, $p<0.01$).

3.4. Criteria of diagnostics for endothelium-dependent risk factors for the development of essential arterial hypertension in children based on the associations of clinical, hemodynamic, and immunological parameters

According to the diagnosis of endothelium–dependent (ED) risk factors for the formation of EAH in children in the analyzed cohorts the relationships (associations) of the frequency of detection and severity of ED risk factors for the formation of EAH were investigated by calculating the relative risk RR (relative risk is a measure of the association between the presence of a factor and the effect, showing how many times the probability of EAH among children, those exposed to the studied factor is higher than those not exposed to it RR= [a/(a+b)]/[c/(c+d)]) and attributive risk – AR (attributable risk is a measure of association reflecting the absolute effect of exposure, excess risk of disease in those who were exposed to the considered exposure).

AR (attributive risk) in cohort studies is calculated as the difference of cumulative incidents. Using the example of the association of vitamin D deficiency (<20 ng/ml in serum) with the risk of EAH development, AR will be calculated as follows:

AR = [a/(a+b)] - [c/(c+d)]= [34/(34+5)] - [9/(9+38)]=0,68=68/102

At the same time, the excess risk of EAH observed in children with vitamin D deficiency (<20 ng/ml in serum) is 68 cases per 100.

The attributive proportion or etiological fraction of vitamin D3 deficiency in the development of EAH is (Table 7): AR%= (0,68/[34/(34+5)]) x 100%= 78.2%

Table 7.

Relative risk (RR) and attributive risk (AR%) values of the development of essential arterial hypertension in children, linked to the analyzed factors

№	Analyzed factors	Children with HNAP n=42		Children with AH n=43	
		RR	AR%	RR	AR%
1	Vitamin D deficit <20 ng/ml	**2.8**	65.6	**4.6**	**78.2**
2	VDR (G/A)	**2.2**	55.0	**3.3**	69.0
3	0.17< endothelin-1-21 <0.41 fmol/ml	1.4	30.0	2.4	58.0
4	Endothelin 1-21 >0.41 fmol/ml	1.6	36.8	-	**100**
5	0.49<CRP hs <1.19 mg/L	**2.1**	52.2	1.8	46.9
6	CRP hs >1.19 mg/L	**7.3**	**86.8**	**11.1**	**91.0**
7	TH>0.76 mmol/L	1.8	43.3	1.9	46.5
8	LDL>2.69 mmol/L	**2.1**	52.2	1.3	25.4
9	HDL>1.27 mmol/L	1.6	38.3	2.0	50.8
10	TNF-α >2.84pg/mL	1.6	3.3	2.2	54.7
	Ca <2.22 mmol/L	1.4	30.0	1.5	31.3
11	D_{PA} ≥26.7%	1.9	48.3	**3.6**	**72.5**
12	TIM CCA >0.52 mm	1.6	37.9	**3.7**	**72.7**

Therefore, if the level of vitamin D has causal significance in terms of the risk of developing EAH in children aged 14-15 years old, then among children with vitamin D3 deficiency (<20 ng/ml in serum) in 78.2% of cases of EAH disease is associated with the isolated effect of deficient vitamin D levels.

Critical assessment of potentially adverse effects of endothelium–dependent factors in the diagnosis of the risk of EAH development in children established the following indicators of sensitivity (sensitivity, Se) and specificity (specificity, Sp), validity and diagnostic effectiveness of each specific factor (Table 8).

Table 8.

Sensitivity (S_e) and specificity (S_p), with assessment of the validity and diagnostic efficiency of the analyzed diagnostic tests

№	Analyzed factors	Children with HNAP n=42		Children with AH n=43		Validity assessment		Diagnostic efficiency	
		S_e%	S_p%	S_e%	S_p%	HNAP	AH	HNAP	AH
1	Vitamin D_3 deficit <20 ng/ml	61.9	**88.4**	79	**88.4**	50.3	**67.4**	**75.3**	**83.7**
2	VDR (G/A)	16.7	**100**	55.8	**100**	16.7	55.8	58.8	**77.9**
3	0.17< endothelin 1-21 <0.41 fmol/ml	48.8	67.4	72.1	67.4	16.2	39.5	58.8	69.8
4	endothelin 1-21 >0.41 fmol/ml	33.3	**82.7**	**100**	**82.7**	16.0	**82.7**	62.0	**87.8**
5	0.49<CRP hs <1.19 mg/L	66.7	67.4	62.8	67.4	34.1	30.2	67.0	65.1
6	CRP hs >1.19 mg/L	**78.6**	**86.2**	**87.5**	**86.2**	**64.8**	**73.7**	**83.7**	**86.7**
7	TH>0.76 mmol/L	47.6	**79.1**	51.2	**79.1**	26.7	30.3	63.5	65.1
8	LDL>2.69 mmol/L	66.7	67.4	46.5	67.4	34.1	13.9	67.1	57.0
9	HDL<1.27 mmol/L	33.3	44.2	25.6	44.2	-	-	61.2	65.1
10	TNF-α >2.84pg/mL	66.7	55.8	76.7	55.8	22.5	32.5	61.2	66.3
	Ca <2.22 mmol/L	50.0	67.4	51.2	67.4	17.4	18.6	58.8	59.3
11	$Dg_{па}$ ≤26.7	+23.8	+48.8	+11.6	+48.8	-	-	63.5	69.8
12	TIM CCA >0.52 mm	45.2	**76.7**	**79.1**	**76.7**	21.9	55.8	61.2	**77.9**

As an example illustrating the principle of calculating the Se and Sp test indicators with assessment of the validity and diagnostic effectiveness we can cite data from the analysis of the diagnostic significance of determining the level of vitamin D for screening diagnosis of endothelium–dependent risk factors for the development of essential hypertension in children.

The results obtained indicate that potentially adverse effect of a factor such as vitamin D deficiency in the blood when diagnosing the risk of EAH development in children has a fairly moderate sensitivity equal to 79%. Consequently, in 21% of the cases there is a probability that persons with a very high risk of developing the disease will be classified as those with low one. At the same time, this factor has a high specificity, i.e. in 88.4% of the cases positive test results make it possible to correctly diagnose a very high risk of disease development. But the integral assessment of the studied factor showed moderate validity (67.4%) and a fairly high diagnostic efficiency (83.7). Critical assessment of potentially unfavorable endothelium–dependent risk factors for the development of EAH based on associations of clinical, hemodynamic and immunological parameters in children established the following diagnostic tests for diagnostic effectiveness in decreasing importance: endothelin 1-21>0.41 fmol/ml – 87.8, CRPhs >1.19 mg/L – 86.7, vitamin D deficiency <20 ng/ml- 83.7, TIM CCA >0.52 mm – 77.9, Dgpa ≤26.7% – 69.8 6, TNF- α>2.84 pg/ml – 66.3, TH >0.76 mmol/l – 65.1, HDL<1.27 mmol/l – 65.1, LDL>2.69 mmol/l – 57.0.

According to the objective, the developed criteria can be used to diagnose and predict ED in the development of essential arterial hypertension in children (Table 9).

Table 9.

Diagnostic criteria of ED in the development of essential arterial hypertension in children

№	Analyzed parameters	No ED		ED risk		ED
		Very low risk	Low risk	Average risk	High risk	
1	Vitamin D ng/ml	>30		21-30	11-20	<10
2	Endothelin -1-21, fmol/ml	<0.10	≥0.16	0.17-0.30	0.31-0.65	>0.66
3	CRP hs, mg/L	<0.3	0.40-0.48	0.49-0.56	0.57-0.98	>0.99
4	TH, mmol/L	<0.76	0.77-0.99	1.0-1.30	1.31-1.46	>1.47
5	LDL, mmol/L	<2.69	2.69-2.84	2.85-3.0	3.10-3.34	>3.35
6	HDL, mmol/L	>1.27	>1.20	≥1.0	<0.9	
7	DgPA, %	>28.9	≥26.7	24.7-17.2	17.1-15.6	≤15.6
8	TIM CCA, mm	≤0.53		0.54-0.56	0.57-0.64	≥0.65

The abovementioned reliable tests constitute a diagnostic complex for assessing endothelial dysfunction in EAH. The presence of association of diagnostic test data with HNAP makes it possible to predict a high risk of EAH development.

CHAPTER IV. METHOD OF THERAPY AND PREVENTION OF ESSENTIAL ARTERIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

The conducted research on patent and scientific medical literature has found various ways of treating EAH in children and adolescents.

There is known method for the treatment of essential arterial hypertension in adolescents with obstructive sleep apnea/hypopnea syndrome (Patent, RF. No. 0002472535, Mandzyak T.V. et al. Method of treatment of essential arterial hypertension in adolescents with obstructive sleep apnea/hypopnea syndrome). The essence of the treatment method consists in additional nasal noninvasive auxiliary ventilation with constant positive pressure during night sleep (nCPAP therapy) and light therapy with a therapeutic wellness lamp with the background of standard treatment regimens.

The described method of treatment has the following disadvantages:

1. Mandatory availability of expensive nCPAP device with individual nasal masks;

2. Long–term therapy - 8 hours with a night's sleep for 10 procedures monthly in hospital;

3. The occurrence of subjective unpleasant sensations when strengthening a nasal mask, the selection of which is strictly individual;

4. When conducting light therapy the spectrum of the visible light range is not specified, for which there are, as for any physiotherapeutic factor, general and particular contraindications.

Complex treatment of vegetative-vascular dystonia and arterial hypertension in adolescents is well known used method (Patent, RF. No. 0002537312, Mashanskaya A.V. et al. A method of complex treatment of vegetative-vascular dystonia and arterial hypertension in adolescents). The method includes standard therapy, diet, physiotherapy treatment with running, alternating magnetic field and treadmill exercises in hospital.

The disadvantage of this method is time-limited course of physical therapy (treadmill therapy in aerobic mode), which does not take into account physical fitness and reserve heart rate of a teenager.

A method of treating adolescents with essential arterial hypertension is also known (Patent, RF. No. 0002483744, Ilkova V.F. et al. A method of treating adolescents with essential arterial hypertension). This method of treatment involves taking aqueous infusion of phytocomp (Siberian shiksha grass, basil grass, marsh grass, Pallas honeysuckle fruits) and additionally taking oxygen phytococtail

prepared on the basis of this infusion of phytocomp, licorice root extract and syrup with hypotensive and diuretic effect.

However, it is not specified in combination with which other methods of treatment the therapeutic effect is provided. There is a possibility of developing allergic and dyspeptic reactions, which, of course, limits the use of the medicinal collection (Siberian shiksha affects nervous system and can cause unforeseen reactions; basilisks are not recommended for constipation and individual intolerance; Pallas honeysuckle fruits are not recommended for hyperacid gastritis and gastric ulcer).

There is well-known method for the treatment of endothelial dysfunction in children with systemic arterial hypertension and impaired pulmonary hemodynamics (Patent, Eurasian Patent Office. No. 200901627, Agapitov L.I. et al. Method of treatment of endothelial dysfunction in children with systemic arterial hypertension and pulmonary hemodynamic disorders). This method involves administration of L-carnitine diluted with liquid in a daily dose from 50 mg / kg to 2 g. inside 30 minutes before eating for at least one month.

However, the described method of treatment has following disadvantages:

1. There are no clear criteria for the selection of children for the application of this method.

2. There is no monitoring of laboratory markers of endothelial dysfunction in children.

3. The effectiveness of treatment is evaluated only by the parameters of endothelium-dependent vasodilation of the brachial artery.

4. Low specificity of the studied indicators for evaluating the effectiveness of L-carnitine in endothelial dysfunction.

5. When taken orally, the intestinal microflora converts L-carnitine into trimethylamine, which, when oxidized in the liver, turns into trimethylaminoxide. A high level of trimethylaminoxide in blood increases the chance of CVD development.

A method for correcting endothelial dysfunction is also known (Patent, RF. No. 2007125205/14, Potapov V.N. et al. Method of correction of endothelial dysfunction). The method includes together with the background diet dosed physical exertion and smoking cessation, additionally prescribing dietary supplement "Thymarin" in a dose of 5 ml 2 times a day before meals for 21 days. "Thymarin" is a source of antioxidants and vitamin C and is ethanol extract of sea urchin. The active ingredient of this dietary supplement is echinochrome A and ascorbic acid. At the same time, ED correction and improvement of the function of the intercellular matrix

are achieved. However, this method is applicable in adults with coronary heart disease.

There is method for the treatment and prevention of hypertension and pharmaceutical composition for the treatment of hypertension (Patent, RF. No. 0002525156, Sergeeva S.A. et al. A method for the treatment and prevention of hypertension and pharmaceutical composition for the treatment of hypertension). At the same time, effective treatment of arterial hypertension is provided by maintaining pharmaceutical composition containing activated potentiated antibodies to angiotensin II receptor and to endothelial NO synthase. However, this experimental study was conducted on animals.

There is also known method for correcting endothelial dysfunction in a child or teenager with a high level of atherosclerosis risk factors and high normal blood pressure (Patent, Republic of Belarus. No. 20080999, Maksimovich N.A. et al. A method for correcting endothelial dysfunction in a child or adolescent with a high level of atherosclerosis risk factors and high normal blood pressure). At the same time, the authors combine the elimination of controlled risk factors for atherosclerosis from the stereotype of behavior with the use of Undevit a and /or Azelicapsa and /or Enalapril for 2 weeks.

The disadvantage of this method is lack of clear criteria for selecting patients and recommendations for monitoring ED markers.

The abovementioned disadvantages of existing methods of treatment and prevention of EAH in children and adolescents are overcome by the proposed invention.

When conducting a patent search for the method for the treatment and prevention of essential arterial hypertension in children and adolescents using aqueous solution of cholecalciferol - AquaDetrim (vitamin D) at a therapeutic dose of 3000 IU / day with deficiency level of vitamin D (25 (OH)D) in blood serum (<20ng/ml or <50nmol/L) and 2000 IU/day at an insufficient level (21-30ng /ml or 51-75nmol /l) for 1 month, with transition to a preventive dose of 1000 IU / day for 12 months with the background rational DASH diet and appropriate physical activity (PA) of moderate to high intensity, depending on the physical fitness of the child with the calculation of the target range of heart rate (TRHB) was not found.

The objective of the present invention- research was to develop an affordable, effective, simple, not requiring large material and technical costs method for the treatment and prevention of essential arterial hypertension in children and adolescents.

This task was solved by determining the level of vitamin D in blood serum and, depending on its indicators, the appointment of aqueous solution of cholecalciferol AquaDetrim (vitamin D) at a therapeutic dose of 3000 IU/day with deficiency level

(25 (OH)D<20ng/ml or <50 nmol/L) and 2000 IU/day with insufficient level (25 (OH) D = 21-30ng / ml or 51-75nmol / L) for 1 month, with transition to a preventive dose of 1000 IU / day for 12 months with the background rational DASH diet and appropriate physical activity.

Interpretation of the level of 25(OH)D in blood serum of children was carried out in accordance with the National Program of the Russian Federation on the provision of vitamin D [64] (Table 10).

Table 10

Interpretation of 25(OH)D concentrations (2018)

Classification	25(OH)D in blood
Vitamin D deficit	<20 ng/mL (<50 nmol/L)
Vitamin D insufficiency	21-30 ng/mL (51-75 nmol/L)
Adequate vitamin D level	>30 ng/mL (>75 nmol/L)

But vitamin D deficiency <10 ng/ml was characterized as profound vitamin D deficiency according to the classification of vitamin D provision in children and adults in compliance with the recommendations of the Russian Association of Endocrinologists in 2017 (Table 11).

Table 11

Classification of vitamin D supply among children and adults population in compliance with the recommendations of the Russian Association of Endocrinologists (2017)

Classification	25(OH)Din blood, ng/mL (nmol/L)
Profound vitamin D deficit	<10 ng/mL (<25 nmol/L)
Vitamin D deficit	<20 ng/mL (<50 nmol/L)
Vitamin D deficiency	21-30 ng/mL (51-75 nmol/L)
Adequate level of vitamin D	>30 ng/mL (>75 nmol/L)
Levels with possible toxicity of vitamin D	>150 ng/mL (>375 nmol/L)

Clinical study inclusion criteria:

Children with essential arterial hypertension (AH) without target organ damage and children with high normal blood pressure (HNAP). The inclusion criteria were the following: average levels of systolic blood pressure (SAP) and/or diastolic blood pressure (DAP) equal to or exceeding the 95th percentile for given age, gender and height (Russian Recommendations, 2009); high normal blood pressure average values of SAP or DAP between the 90th and 95th percentiles. The age of children is 14-16 years old.

Clinical study exclusion criteria:

The exclusion criteria were congenital kidney abnormalities, endocrine pathology, secondary or symptomatic hypertension, stage II EAH, as well as the age of children younger than 14 years old.

Children with EAH were not treated with antihypertensive drugs.

Evaluation of the results of the study was carried out in groups of children with HNAP and EAH (the basic groups who underwent therapeutic and preventive measures and comparison groups - also children with HNAP and EAH who did not participate in these activities) after 1, 6, and 12 months with repeated paraclinical studies.

Markers of ED in this study were the following: serum levels of endothelin 1-21, vitamin D (25 (OH)D), high-density lipoproteins (HDL) and low-density lipoproteins (LDL), triglycerides, highly sensitive CRP (CRP-hs), as well as indicators of duplex scanning of the right and left common carotid arteries and brachial artery: Dba – increase in the diameter of the brachial artery (BA) after the 3rd minute of decompression with endothelium-dependent vasodilation (test with reactive hyperemia) in % and TIM CCA – the total average thickness of the intima-media complex of the common carotid artery in mm.

For critical assessment of potentially favorable factors of the impact of therapeutic and preventive measures, such as the appointment of AquaDetrim in therapeutic and preventive doses with rationalization of nutrition according to the DASH diet and optimization of FA individually for each child, the clinical efficacy index was calculated as percentage for EAH and HNAP [26]. Positive efficacy [26] of vitamin D treatment was evaluated for each diagnostic marker of ED in relation to the comparison group. The positive efficacy of treatment was significant at a value of PF>1.0.

In the main group and the comparison group for each child individually taking into account the diagnostic markers of ED and the level of vitamin D (deficiency or insufficiency) the following measures were developed and carried out:

- a plan was drawn up to correct the level of vitamin D with the help of aqueous solution of cholecalciferol AquaDetrim: with deficient level of vitamin D_3, the daily therapeutic dosage was 3000 IU / day, and with insufficiency 2000 IU / day for 1 month, with the transition to a preventive dosage of 1000 IU for 12 months. Therapeutic and prophylactic doses of AquaDetrim were calculated in accordance with the National Program of the Russian Federation on Vitamin D provision [64].

- correction of nutrition; the number of servings per day with the equivalent portion sizes of the DASH diet (DASH Eating Plan. National Heart, Lung, and Blood Institute. Available at: https://www.nhlbi.nih.gov/health-topics/dash-eating-plan .);

- assessment and correction of physical activity from moderate to high intensity, depending on the physical fitness of the child with the calculation of the TRHB [55].

Monitoring of the implementation and execution of the developed program of therapeutic and preventive measures was carried out by interviewing the children themselves and their parents, keeping a nutrition diary, PA and home monitoring of blood pressure.

The criteria for evaluating clinical effectiveness of therapeutic and prophylactic therapy were considered to be the duration of therapy necessary to obtain clinical effect: normalization of vitamin D levels and reduction of the risk of ED, normalization of SAP and DAP indicators <90 percentile for a given age, gender and height of children.

Table 12 shows positive efficacy (PF) of vitamin D treatment for 1 month in children with HNAP and EAH.

As evidenced by the data presented in Table 12, AquaDetrim therapy performed during the month showed positive effect with reliable values.

More significant (PF=3.1) was the indicator in the group of children with EAH of decrease in the factor of endothelin 1-21≥0.66 fmol/ml when corrected with vitamin D. But with the factor 0.31≤ Endothelin 1-21 ≤0.65 fmol/ml in the group with HNAP this indicator was 2.4, indicating longer use of the therapeutic dosage of the drug. Pronounced positive efficacy was established by reducing the level of the factor of CRP-hs >1.19 mg/ (PF=2.3) in the main and 0.98<CRP-hs <1.19 mg/L (PF=2.8) in the group of children with HNAP. Increase in the level of HDL>1.0 mmol/L was less expressed in the groups with HNAP and EAH (PF=1.7 and 1.1, respectively).

The results obtained by us are consonant with the literature data.

A study involving Spanish schoolchildren showed that the serum content of 25 (OH)D was inversely proportional to the level of triglycerides [128]. A large-scale cross-sectional study from Finland, conducted to study the relationship between the content of 25(OH)D, 1.25(OH)2D and dyslipidemia, revealed that low levels of 1.25(OH)2D correlated with low HDL content, low levels of 25(OH)D correlated with high content of total cholesterol, LDL and triglycerides [112].

The results of duplex scanning of BA and right, left CCA showed reliable positive efficiency, although the PF values were not so pronounced.

The thickness of the intima-media complex (TIM) of the common carotid artery (CCA) is currently a sonographic marker of early atherosclerotic lesion of the vascular wall and reflects local changes in the carotid arteries.

Table 12

Positive efficacy (PF) of the treatment with vitamin D for 1 month in the examined children (PF, Kelmanson I.A., 2004)

№	Analyzed factors	Positive efficacy (PF) Of the treatment with vitamin D (AquaDetrim)	
		Children with HNAP n=20	Children with AH n=17
1	Vitamin D deficit <20 ng/ml	2.4	2.2
2	Vitamin D deficiency 20-30 ng/ml	2.6	2.8
3	0.31≤ endothelin 1-21 ≤0.65 fmol/ml	2.4	-
4	Endothelin 1-21 ≥0.66 fmol/ml	-	3.1
5	0.98<CRP hs <1.19 mg/L	2.8	-
6	CRP hs >1.19 mg/L	-	2.3
7	1.31≤TH≤1.46 mmol/L	1.8	-
8	TH>1.47 mmol/L	-	1.6
9	3.1≤LDL≤3.34 mmol/L	1.6	-
10	LDL>3.35		1.5
11	HDL>1.0 mmol/L	1.7	1.1
11	17.1≤$D_{BA\ GROWTH}$≥15.6 %	1.6	-
12	$D_{BA\ GROWTH}$≤15.6 %	-	1.3
13	0.57≤TIM CCA ≤0.64 mm	1.3	-
14	TIM CCA ≥0.65 mm	-	1.9
15	SAP and DAP <90 percentile	2.2	2.1

TIM correlates with the level of glycemia and atherogenic lipid profile. The earliest non-lipid stage of atherosclerotic process is thickening of the intima of vessels, due to the proliferation of smooth muscle cells, elastic and collagen fibers. At the next stage lipid spots and stripes appear, which are located in different parts of the arterial system and are not an obstacle to blood circulation. Children and adolescents are characterized by asymptomatic course of atherosclerotic process without clinical manifestations. The latent phase of coronary atherosclerosis can last 20 years or more. In the PDAY study (Pathobiological Determinants of Atherosclerosis in Youth) and Bogalusa Heart Study, which studied the manifestations of atherosclerosis in children, adolescents and young people who died as a result of accidents, a close correlation was established between the level of

blood pressure (BP), lipids, glycated hemoglobin, body mass index (BMI), smoking and the severity of atherosclerotic process in aorta and coronary arteries.

Verdoia, M. et al. proved that the direct effect of vitamin D on the arterial wall can protect against atherosclerosis by reducing the absorption of cholesterol by macrophages and formation of foam cells, reducing the proliferation of smooth muscle cells of blood vessels and reducing the expression of adhesion molecules in endothelial cells [143].

Vitamin D deficiency directly affects the muscle wall of blood vessels, leading to increased vascular resistance, increase in the intima-media complex (IM), which was convincingly shown in the work of Sugden J.A. et al. (2008) [137]. At the same time, there was improvement in blood pressure and endothelial function in patients with type 2 diabetes mellitus who received vitamin D once at a dose of 100,000 IU.

The indices of the clinical effectiveness of the analyzed exposure factors, depending on the duration of therapy, are presented in Table 13.

Table 13.

Indices of clinical effectiveness and HNAP and EAH prevention with the help of vitamin D, due to ED correction dependently on the duration of the therapy (%)

№	Analyzed factors	Clinical effectiveness in 1 month		Clinical effectiveness in 6 months		Clinical effectiveness in 12 months	
		HNAP	AH	HNAP	AH	HNAP	AH
1	ED high risk	77.1	-	89.2		99.2	
2	ED	-	53.1		73.8		89.3

Note: *ED high risk* in case of vitamin D =20-30 ng/ml, endothelin 1-21- 0.31-0.65 fmol/ml, CRP-hs=0.99-1.19 mg/L, TH =1.31-1.46 mmol/L, LDL = 3.16-3.34 mmol/L, HDL<0.9 mmol/L, 17.1≤$D_{ba\ growth}$ ≥15.6%, 0.57≤TIM CCA ≤0.64 mm. *ED* in case of vitamin D<20 ng/ml, endothelin 1-21 ≥0.66 fmol/ml, CRP-hs >0.99 mg/L,TH>1.47 mmol/L, LDL>3.35 mmol/L, HDL<0.9 mmol/L, $D_{BA\ GROWTH}$≤15.6%, TIM CCA ≥0.65 mm

The results obtained indicate that the potentially beneficial effects of the factors after 6 and 12 months, such as the use of a therapeutic dose of AquaDetrim for a month and the transition to a preventive dose in subsequent months, reach high values of CEI.

Moreover, the reduction of high risk and pronounced ED occurs at the maximum rate in the period after 6 months. Consequently, the maximum clinical

effectiveness is achieved with the long-term use of the developed ED correction program and vitamin D levels in combination with rational nutrition according to the DASH diet [91] and PA.

Thus, the long-term use of the abovementioned therapeutic and preventive measures led to the restoration of the target level of SAP and DAP in children with HNAP and EAH and decrease in the severity of ED by 99.2 and 89.3%, respectively.

The effectiveness of the developed method of treatment and prevention of EAH in children is shown by the following examples:

Example 1. Oybek M., 14 years old. He was being examined at Juvenile dispensary.

Diagnosis: essential arterial hypertension, first stage.

Complaints of headaches, sleep disorders and increased blood pressure up to 140/80 mmHg.

According to anamnestic data: a child from the 1st pregnancy, which progressed without peculiarities. Physiological delivery at 39 weeks. Birth weight 2510 g., height 53cm, screamed immediately. Feeding was on formula. Up to 2 years old body mass index (BMI) Z on the median +3CO. Later, he grew and developed according to his age. Burdened heredity by 1 and 2 degrees of maternal kinship.

Physical examination: the condition is relatively satisfactory. Weight-57 kg, Height- 164cm, BMI- 21.2 kg/m2 (Z value: between medians 0 and +1CO (standard deviation according to growth and development curves, WHO, 2007), blood pressure 140/80 mmHg. Asthenic physique, posture disorder (stoop). The lymph nodes are not enlarged. Pathology has not been detected for internal organs and systems. Sexual development corresponds to the age.

Blood and urine analysis without pathological changes. Carbohydrate metabolism is not disturbed.

ECG: sinus rhythm, moderate sinus tachyarrhythmia heart rate - 84-95. EOS is the normal position. Syndrome of early ventricular repolarization.

Consultation of an optometrist: fundus without pathology.

Consultation of a neurologist: focal neurological pathology was not detected.

Biochemical and immunological blood tests were performed on the lean, as well as duplex scanning of the right and left common carotid arteries and brachial artery with the calculation of the following: total average thickness of intima-media complex of the common carotid artery in mm., and Dba, increment–the diameter of brachial artery increment (BA) with endothelium-dependent vasodilation (test with reactive hyperemia) after the 3rd minute of decompression, in %.

According to baseline levels of vitamin D, Endothelin 1-2, CRP-hs, lipid spectrum and ultrasound of BA and TIM CCA (Table.14) it was found that there was ED. In this connection the patient was prescribed: AquaDetrim at a dose of

3000ME / day (6 drops) a course of 1 month, with a transition to a preventive dose of 1000 IU / day (2 drops) for 12 months, nutrition according to the DASH diet and PA (swimming, under the supervision of an instructor 3 times a week for 1 hour, for 1 month CDR = 130 to 154 beats / min, corresponding to moderate intensity PA, then TRHB = from 155 to 185 beats/min., intensive PA.

The results of the studies are presented in Table 14.

Table 14.

Dynamics of the studied parameters

№	Analyzed parameters	Original level	In 1 month	In 6 months	In 12 months
1	Vitamin D (25(OH)D) ng/ml	11	25.1	30.2	31.5
2	Endothelin-1-21, fmol/ml	0.67	0.30	0.17	0.12
3	CRP hs, mg/L	1.2	0.67	0.54	0.41
4	TH, mmol/L	1.48	1.3	0.99	0.97
5	LDL, mmol/L	3.36	2.9	2.71	2.67
6	HDL, mmol/L	0.9	1.0	1.2	1.2
7	$D_{BA\ GROWTH}$, %	15.6	16.5	18.6	21.5
8	TIM CCA, mm	0.64	0.53	0.48	0.46
9	SAP, mm Hg	140	130	125	120
10	DAP, mm Hg	80	75	75	75

Taking into account the results obtained conclusion was made about the effectiveness of the developed method of treatment and prevention of EAH that the level of vitamin D reaches adequate values by 6 months, endothelial function is restored (according to ultrasound, the ability of endothelium to vasodilation increases by 37.8%, TIM CCA decreases by 28.1%), SA3 and DA3 reach normal values in 6 months and are stabilized.

Example 2. Ibrohim M., 15 years old. He was being examined at Juvenile dispensary.

Diagnosis: HNAP.

He didn't file complaint.

According to anamnestic data: the child from the 2nd pregnancy, which progressed without peculiarities. Physiological childbirth at 39-40 weeks. Birth weight 3510 gr., height 54cm, screamed immediately. Exclusively breastfeeding up

to 6 months. Up to 2 years of ag, BMI - Z was at a median between 0 and +1CO. Later, he grew and developed according to his age. Burdened heredity by 1 degree of maternal kinship.

Physical examination: the condition is satisfactory. Weight-58.5 kg, Height-166cm, BMI- 21.0 kg/m^2 (Z value: between medians 0 and +1CO (standard deviation according to growth and development curves, WHO, 2007), blood pressure 130/80 mmHg. Normal build, flat feet 1 art. The lymph nodes are not enlarged. Pathology has not been detected in internal organs and systems. Sexual development corresponds to the age.

Blood and urine analysis without pathological changes. Carbohydrate metabolism is not disturbed.

ECG: sinus rhythm, heart rate - 76-85. EOS is the normal position.

Consultation of an optometrist: fundus without pathology.

Consultation with a neurologist: focal neurological pathology was not detected.

Biochemical and immunological blood tests were performed, as well as duplex scanning of the right and left common carotid arteries and brachial artery.

According to baseline levels of vitamin D, Endothelin 1-2, CRP-hs, lipid spectrum and ultrasound of BA and TIM CCA (Table.15) it was found that there was a high risk of ED.

Table 15.

Dynamics of the studied parameters

№	Analyzed parameters	Original level	In 1 month	In 6 months	In 12 months
1	Vitamin D (25(OH)D) ng/ml	20.0	30.1	30.3	32.5
2	Endothelin-1-21, fmol/ml	0.47	0.23	0.16	0.12
3	CRP hs, mg/L	1.10	0.57	0.50	0.41
4	TH, mmol/L	1.38	1.30	0.99	0.97
5	LDL, mmol/L	3.16	2.81	2.69	2.67
6	HDL, mmol/L	0.9	1.0	1.27	1.27
7	$D_{BA\ growth}$, %	16.7	18.5	20.6	24.5
8	TIM CCA, mm	0.58	0.53	0.51	0.51
9	SAP, mm Hg	130	125	120	120
10	DAP, mm Hg	80	75	75	75

In this connection, the patient was prescribed: AquaDetrim at a dose of 2000 MG / day (4 drops) the course is 1 month, with the transition to a preventive dose of 1000 IU / day (2 drops) for 12 months, nutrition according to the DASH diet and PA (cycling 16-18 km /h 3 times a week for 1 hour, for 1 month TRHB = from 128 to

152 beats / min, corresponding to PA moderate intensity, then cycling 19-20 km /h 3 times a week for 1 hour TRHB = from 153 to 184 beats /min., intense PA.

The results obtained indicate the effectiveness of the developed method: the level of vitamin D reaches adequate values by the end of the 1st month, the endothelial function is preserved (the high risk of ED is reduced to very low; according to ultrasound, the ability of the endothelium to vasodilation increases by 46.7%, TIM CCA decreases by 12.1%), SAP and DAP reach normal values in 6 months and are stabilized.

The proposed method has been tested in a polyclinic and has proven to be an effective method of treatment and prevention of essential arterial hypertension in children and adolescents that does not require large material and technical costs. Patent No. IAP 06992 (27.06.2022, valid until 20.08.2024) was obtained for this method of treatment and prevention of essential arterial hypertension in children and adolescents.

CONCLUSION

Arterial hypertension in children and adolescents has acquired a basis in cardiovascular medicine thanks to progress in pathophysiological and clinical studies. The lack of standardized methodology for assessing and monitoring blood pressure, taking into account the gender, age and height of children and adolescents in our republic, does not allow us to realistically assess the state of children's health and the situation with the prevalence of hypertension among the child population. Late diagnosis and inadequate assessment of the prognosis of hypertension in children and adolescents underlie high morbidity and mortality rates in older age groups, and the success of preventive programs directly depends on their early implementation. The positive experience of countries with low mortality rate from CVD shows that the success of the fight against this pathology is greatly influenced by its early detection, treatment and prevention in childhood. In this regard, the development and implementation of screening methods for the diagnosis and prevention of hypertension in children and adolescents at the primary health care level is extremely important.

The analysis of average parameters of the CRPhs level in children revealed the highest level of CRPhs in children with stable hypertension with significant difference compared to the control ($p<0.05$). Significantly elevated values of the level were also noted in children with LAH ($p<0.05$) and HNAP ($p<0.05$) in relation to the parameters of the children with normal blood pressure. The range of individual CRPhs values was large and varied from 0.01 to 4.71 mg/l. Our clinical studies have shown that as the blood pressure values increased, the level of the proinflammatory cytokine TNF-α increased, with statistically significant difference in relation to the control in the groups of children with LAH and SAH. But the concentration of anti-inflammatory IL-10 did not decrease.

It was revealed that at rest the average diameter of the BA in children with hypertension was 2.45 ± 0.19 mm, which is 4.3% and 3.2% less than in healthy children and children with high normal blood pressure (HNAP). Analysis of the dynamics of changes in the diameter of the brachial artery (BA) and the linear velocity of blood flow in a sample with endothelium-dependent vasodilation showed that significant increase in the diameter of the BA in children with LAH and SAH was 1.2 and 1.1 times less compared with groups 1 and 2 ($p<0.001$, $p<0.001$, respectively, in relation to the control). A similar trend is observed in endothelial vasodilation of BA ($p<0.01$, $p<0.001$, respectively, for groups 3 and 4), which indicates violation of the ability of BA to relax and increase blood flowalready at the initial stages of the development of hypertension in children.

Statistically significant thickening of TIM was found in children of the basic groups according to the general average values (0.66±0.04 and 0.67±0.05 mm, respectively, for groups 3 and 4) against the control and comparative groups (0.50±0.026 mm; $p<0.001$, 0.56±0.03; $p<0.001$, respectively). Systolic blood flow rate also tended to increase by 3.3%, 4.3%, respectively, in children with LAH and SAH and by 1.9% in children with HNAP in relation to the control. The parameters of the diameter of the CCA in the systole (D CCA) and diastole (D CCA) in children of the basic groups were significantly reduced in relation to the control and comparison group.

Disorders of the vasodilating function of the endothelium (Dg) and the thickness of the intima-media CCA (TIM CCA) are associated with immunological determinants of ED and atherogenic factors, namely with the levels of CRPhs, TNF-α, IL-10 and E-1-21, 25 (OH)D and the content of TH, HDL and LDL.

The study and assessment of the provision of schoolchildren with vitamin D showed that only 13.4±3.8% of children had an optimal level of vitamin D with average level of 25 (OH)D 31.1±0.39ng/ml. Significantly high frequency of insufficient content (28.0±4.9%, $p<0.05$), vitamin D deficiency (32.9±5.2%, $p<0.05$) and pronounced vitamin D deficiency (25.6±4.8%, $p<0.05$) was established. According to the average vitamin D content in children deficiency level was established (17.7 ± 0.89 ng/ml). The analysis of the provision of schoolchildren with vitamin D, depending on blood pressure indicators, established significantly high frequency of vitamin D deficiency in children with high blood pressure ($p<0.01$) and hypertension ($p<0.01$) in relation to children with normal blood pressure. The diagnostic test of vitamin D deficiency for the group of children with HNAP and LAH had high sensitivity (90%), moderate specificity (68%) and relative risk RR=11.25, for children with SAH, respectively, 89% sensitivity and 70% specificity with RR= 10.0.

Pronounced deficiency was noted in children with HNAP and hypertension with significantly high frequency in the main groups with respect to the comparison group $p<0.01$ and $p<0.01$, respectively, in the 1st, (Se=0.75, Sp=0.61, RR=3.0) and in the 2nd, (Se=0.75, Sp=0.65, RR=3.3,) in the main groups.

The study of the level of endothelium-dependent vasoconstrictor factor endothelin – 1-21 (E-1-21) showed significant increase in its serum values in children with HNAP (0.27±0.05 fmol/ml, $p<0.05$) and arterial hypertension (0.42±0.1 fmol/ml, $p<0.05$ and 0.59±0.1 fmol/ml, $p<0.001$, respectively, in the groups of children with LAH and SAH) compared with the control (0.13 ± 0.02 fmol/ml). The frequency of E-1-21 levels >0.26 and >1.0 fmol/ml in children with SAH was 2.4 and 1.6 times higher, respectively (OR=2.4; RR=1.5 and OR=1.6; RR=1.5, respectively) than in children with LAH. But in children with HNAP the

prevalence of E-1-21 levels >0.26 fmol/ml was identical compared to the group of children with SAH (60.0±10.9%, versus 61.1±11.5%, respectively), which indicated early signs of ED in children with high normal blood pressure. This test has 100% sensitivity and 0% specificity in the early diagnosis of ED. In the mechanism of EAH development in children interdependence was revealed between vitamin D deficiency and the severity of endothelial dysfunction at the level of E-1-21 ($r=-0.79$, $p<0.001$), as well as the priority effect of vitamin D availability on the level of DAP ($r=-0.64$, $p<0.01$) in the group of children with LAH, but in in the group of children with SAH this effect was directed to the parameters of systolic blood pressure ($r=-0.6$, $p<0.01$).

Critical assessment of potentially unfavorable endothelium–dependent risk factors for the development of EAH based on associations of clinical, hemodynamic and immunological parameters in children established the following diagnostic tests for diagnostic effectiveness in decreasing importance: endothelin 1-21>0.41 fmol/ml – 87.8, CRPhs >1.19 mg/L – 86.7, vitamin D deficiency <20 ng/ml- 83.7, TIM CCA >0.52 mm – 77.9, Dgpa ≤26.7% – 69.8 6, TNF- α>2.84 pg/ml – 66.3, TH >0.76 mmol/l – 65.1, HDL<1.27 mmol/l – 65.1, LDL>2.69 mmol/l – 57.0.

The abovementioned reliable tests constitute a diagnostic complex for assessing endothelial dysfunction in EAH. The presence of association of diagnostic test data with HNAP makes it possible to predict high risk of EAH development.

Thus, in the pathogenesis of EAH special place is given to violation of the endothelial function of the vascular wall, which not only precedes the development of the disease, but also contributes to its further progression. This fact determines the need for early diagnosis of ED, as well as preventive and therapeutic effects of it. The continuation of studies aimed at reducing arterial stiffness and ED, which are preventive in relation to the development of CVD and their complications also seems promising.

The adaptive response of the vascular system is determined by the state of endothelial function and the level of its molecular regulation, which provides the necessary physiological optimum. In this regard properly organized process of vital activity of the body, namely, rational healthy diet, proper physical activity initiates the function of endothelium. For example, decrease in cholesterol and LDL leads to restoration of endothelium, especially when ED is just being formed and the manifestations are unstable. At the same time, promotion of a healthy lifestyle among children, when stereotype of behavior has not yet developed, seems to be the most promising. The possibility of limiting oneself in childhood to non-drug methods of influencing risk factors for the formation of EAH is attractive, cost-effective and effective.

Method for the treatment and prevention of essential arterial hypertension in children and adolescents includes the introduction of aqueous solution of vitamin D – cholecalciferol (AquaDetrim) at a therapeutic dose of 3000 IU / day with deficient level of vitamin D (25 (OH)D) in blood serum (<20ng/ml or <50nmol/l) and 2000 IU/day at insufficient level (21-30ng /ml or 51-75nmol / l) for 1 month, with a transition to a preventive dose of 1000 IU / day for 12 months with the background rational DASH diet corresponding to moderate to high intensity physical activity, depending on the physical fitness of the child with the calculation of the target range heart rate. The method makes it possible to achieve more effective treatment and prevention of essential arterial hypertension in children and adolescents by correcting the level of vitamin D and endothelial dysfunction with decrease in systolic (SAP) and diastolic (DAP) blood pressure with stabilization of their indicators at the level of normal values corresponding the age, gender and height of the child. This method has no side effects and contraindications for children and adolescents. Patent No. IAP 06992 (27.06.2022, valid until 20.08.2024) was obtained for this method of treatment and prevention of essential arterial hypertension in children and adolescents.

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LIST OF ABBREVIATIONS

BP - blood pressure
ACE –Angiotensin converting enzyme
WHO – World Health Organization
HNAP – high normal blood pressure
DAP – diastolic blood pressure
ED – endothelial dysfunction

IHD - ischemic heart disease
IL-10 - interleukin – 10
IR or RI - Index of resistivity of Purcelo (IRili RI) IR=(LSS-LDS)/LSS
LAH – labile arterial hypertension
IM – intima-media complex
CCA – common carotid artery
BA – brachial artery
PI - Gosling Pulsativity Index (PI or PI) PI=(LSS-LDS)/LS (sred)
SAP – systolic blood pressure
SAH – stable arterial hypertension
SAS - sympatho-adrenal system
CVD – cardiovascular diseases
MTABF - the maximum time-averaged blood flow rate
TIM – thickness of the intima-media complex
TIM av – the average thickness of the intima-media complex
TIM max – maximum thickness of the intima-media complex
Tim CCA av – the average thickness of the intima-media complex of the common carotid artery
TIM CB av - average thickness of the intima-media complex in the area of carotid bifurcation
TIM CB max - maximum thickness of the intima-media complex in the area of carotid bifurcation
TIM CCAg - thickness of the intima-media complex of the right common carotid artery in mm
TIM CCAl - thickness of the intima-media complex of the left common carotid artery in mm
TIM CCAsh – the total average thickness of the intima-media complex of the common carotid artery in mm
Ultrasound – ultrasound examination
USDG – ultrasound Dopplerography
TNF-α - Tumor Necrosis Factor – alpha
TRHB – target range of heart rate
EAH - essential (primary) arterial hypertension
EDV – endothelium-dependent vasodilation
EDV% - BA diameter in endothelium-dependent vasodilation in %
EIV%- BA diameter with endothelium-independent vasodilation in %
AR - attributable risk –attributive risk
CRP hs - highly sensitive C reactive protein
D CCAs - the diameter of the CCA in the systole in mm

D CCAd- the diameter of the CCA in the diastole in mm
D CCA- change in the diameter of the common carotid artery per cardiac cycle (%)
VCCA - systolic blood flow rate
Dº - the initial diameter of the BA in mm
D 30 - BA diameter at 30 seconds of decompression in mm
D 60 - BA diameter at 60 seconds of decompression in mm
D 90 - BA diameter at 90 seconds of decompression in mm
D 3' is the diameter of the BA at 3 minutes of decompression in mm
Dg - increase in the diameter of the BA in %
D max, EDV - BA diameter in endothelium-dependent vasodilation (test with reactive hyperemia)
D max, EIV - BA diameter at endothelium-independent vasodilation (nitroglycerin test)
RR - relative risk – relative risk
Vps or Max. LSS - peak systolic blood flow rate in cm/sec
Vpd or Max. LDS - peak diastolic blood flow rate in cm/sec