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Increased neopterin concentration in patients with primary arterial hypertension

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ABSTRACT

Introduction. The data on the safety profile of anti-tumor necrosis factor (anti-TNF) therapy in real-life patients cohorts with inflammatory bowel disease (IBD) still are lacking.
Neopterin is a pteridine derivative produced from guanosine triphosphate mainly by activated monocytes and macrophages in response to cytokines produced by T-lymphocytes and natural killer cells. Changes in neopterin level reflect the stage of activation of cellular immune system and can be associated with various diseases. Low-grade inflammation is also an important factor in the pathophysiology of hypertension. In presented study we assessed neopterin concentration in 63 patients with primary arterial hypertension compared to 14 control healthy volunteers. Obtained results confirmed increased neopterin level in patients group.

Keywords: neopterin, hypertension, inflammation.

Introduction

Neopterin (2-amino-4-hydroxy-6-(D-erythro-1′,2′,3′-trihydroxypropyl)-pteridine) is a pteridine derivative produced from guanosine triphosphate by activated monocytes, macrophages, dendritic cells, and endothelial cells and to a lesser extent in renal epithelial cells, fibroblasts, and vascular smooth muscle stimulated by interferon gamma. Because it is released in response to cytokines produced by T-lymphocytes and natural killer cells, neopterin is an indicator of activation of cell mediated immunity [1–2]. Neopterin can be assessed in blood serum, plasma, urine, cerebrospinal fluid, pancreatic juice, saliva and gastric juices. Neopterin is a light-sensitive substance, so probes collected for measurement must be protected from light. Physiological serum concentration is lesser than 10 nmol/L and is different in various age groups (**Table 1**) [21]. Other factors that can influence neopterin level include gender, race, BMI, and percentage of body fat. [3]. Changes in neopterin level reflect the stage of activation of cellular immune system and can be associated with various diseases. For example, increase neopterin level was observed in patients with coronary artery diseases and was associated with the progression of the disease [4–5]. Therefore, the inflammation system, in association with other cardiovascular pathways, can be the central pathway in the development and progression of cardiovascular diseases [6].

Essential hypertension can be characterized by increased peripheral vascular resistance to blood flow and is one of important risk factors for developing cardiovascular disease [7]. Most of this resistance results from resistance arteries, which are vessels with lumen diameters < 400 µm [8]. These arteries undergo structural, mechanical or functional vascular remodeling in hypertensive patients – a process that involves extracellular matrix deposition and inflammation. In case of chronic vasoconstriction the vessels may become embedded in the remodeled extracellular matrix and

Table 1. Average neopterin concentration in various age groups

Age (years)	Average neopterin concentration [nmol/L]
< 18	6.8 ± 3.6
19–75	5.3 ± 2.7
> 75	9.7 ± 5.0

may not return to their vasodilated state. Moreover, endothelial dysfunction – an early determinant in the development of hypertension may also participate to the increased vascular tone in hypertension with reduced vasodilation associated with proinflammatory and prothrombotic state [9]. Chronic low-grade inflammation has been recently mentioned to be an integral part in the pathogenesis of vascular disease [10]. Several clinical studies have revealed that pro-inflammatory markers, such as IL-6, ICAM-1 or CRP may be independent risk factors for the development of hypertension [9]. Neopterin is one of inflammatory mediators, which role in hypertension has not yet been sufficiently studied. Numerous studies have confirmed the usefulness of neopterin level measurement in such cases as transplant rejection, viral infections, intracellular bacteria infections, coronary artery disease, angina pectoris and some autoimmune diseases (arthritis, type 1 diabetes, Crohn's disease, autoimmune thyroiditis) [11]. As mentioned earlier, low-grade inflammation is an important factor in the pathophysiology of hypertension. Therefore, the aim of the study was to assess neopterin level in patients with primary arterial hypertension.

Material and methods

63 patients (31 men, 32 women) with primary arterial hypertension, aged from 25 to 67 years (mean: 50.37; standard deviation: 10.58) were enrolled to the study. Patients' weight ranged from 59 to 167 kg (mean: 98.15; standard deviation: 21.50). Patients with acute coronary syndrome, cancer, heart failure, severe renal failure, severe hepatic insufficiency or pregnancy were excluded from the study. The control group consisted of 14 healthy volunteers (6 men, 8 women), aged from 25 to 59 years (mean: 42.57, standard deviation: 11.80), weighed from 50 to 83 kg (mean: 65.21; standard deviation: 9.18). Arterial blood pressure was measured in both groups. Blood samples were collected from elbow vein for biochemical measurements. Neopterin level was assessed using ELISA immunoassay (DRG International Inc., USA). Statistical analyses were carried out using Statsoft Statistica 10.0 software. Normality of distribution was tested with Shapiro-Wilk Test. Statistical significance was assessed using Mann-Whitney U test.

Results

Estimated sample size for statistical power = 0.95 was 56 individuals. Shapiro-Wilk test of normality revealed that most of studied parameters (including neopterin) did not have normal distribution (**Table 2**). As a result, non-parametric Mann-Whitney U test was chosen as a measure of statistical significance ($p < 0.05$).

Table 2. Anthropometric and biochemical characteristic of the participants

	Patients			Controls			Normality of distribution	P
	N	Mean	Standard deviation	N	Mean	Standard deviation		
Age [years]	63	50.37	10.58	14	42.57	11.80	no	**0.029**
Weight [kg]	63	98.15	21.50	14	65.21	9.18	no	**0.000**
Height [cm]	63	169.94	9.16	14	168.50	9.09	no	0.644
BMI [kg/m^2]	63	33.95	6.90	14	22.91	2.03	no	**0.000**
Waist [cm]	63	111.40	16.04	14	73.43	3.50	yes	**0.000**
Hips [cm]	63	114.56	14.19	14	93.71	5.53	yes	**0.000**
SBP [mmHg]	63	158.49	29.16	14	110.36	6.34	no	**0.000**
DBP [mmHg]	63	91.98	11.20	14	72.50	5.46	no	**0.000**
Creatinine [µmol/L]	63	81.68	16.31	14	70.50	10.38	no	**0.015**
Tchol [mmol/L]	63	5.84	1.36	14	5.11	0.61	yes	**0.019**
LDL [mmol/L]	63	3.70	1.13	14	2.76	0.61	yes	**0.002**
HDL [mmol/L]	63	1.19	0.32	14	1.65	0.32	no	**0.000**
TG [mmol/L]	63	2.13	0.88	14	1.02	0.39	no	**0.000**
Glucose [mmol/L]	63	5.09	0.42	14	4.99	0.47	no	0.373
CRP [mg/L]	63	5.73	4.44	14	2.51	1.80	no	**0.001**
ESR [mm/h]	63	9.24	5.65	14	6.64	4.97	no	0.104
ALAT [U/L]	63	34.05	16.38	14	26.57	9.19	no	0.109
ASPAT [U/L]	63	29.41	15.35	14	20.64	3.37	no	**0.002**
Neopterin [nmol/L]	63	6.50	2.510	14	5.17	0.72	no	0.001

Anthropometric and biochemical characteristic of the participants is presented in **Table 2**. Patients and control groups did not differ in height, glucose, ESR and ALAT. Statistically significant differences between these groups were observed for such parameters as: age, weight, BMI, waist and hips circumference, blood pressure, creatinine, total cholesterol, LDL and HDL fraction, triglycerides, CRP, ASPAT and neopterin level. Higher level of neopterin was observed in patients with hypertension compared to healthy controls (**Figure 1**).

Discussion

According to WHO data, approximately 20% of adults (1 billion people in the world) are estimated to have hypertension, defined as blood pressure > 140/90 mm Hg. In the elderly, the prevalence of hypertension can be up to 50% [12]. For example, in the United States 1 per 3 adults have hypertension, while the prevalence increases to 50% for people aged 60 – 69 years and to 75% for patients older than 70 years [13].

Essential hypertension is a multifactorial disease caused by combined action of genetic, environmental, and behavioral factors. A pro-hypertensive change in a single factor can be probably compensated by other control mechanisms. However, any significant disturbance in the balance between the factors which increase and normalize the blood pressure can result in development of essential hypertension [14]. One of the factors which can contribute to the development of hypertension is inflammation [15]. Inflammatory cells accumulate in kidneys and vasculature of patients with hypertension. It was observed in animal models that loss of adaptive immune cells decreases the blood pressure response to such stimuli as ANG II, high salt, and norepinephrine. Moreover, agonistic antibodies to ANG II receptor (produced by B-cells) contribute to hypertension in experimental models of preeclampsia. Also, production of cytokines, such as TNF-α, interleukin-17, and interleukin-6 influences hypertension, possibly due to effects on both the kidney and vasculature. The innate immune system also appears to contribute to hypertension. Therefore, studies concerning immune cell activation could be helpful in understanding this disease [16]. There are only few studies trying to evaluate neopterin level in hyperten-

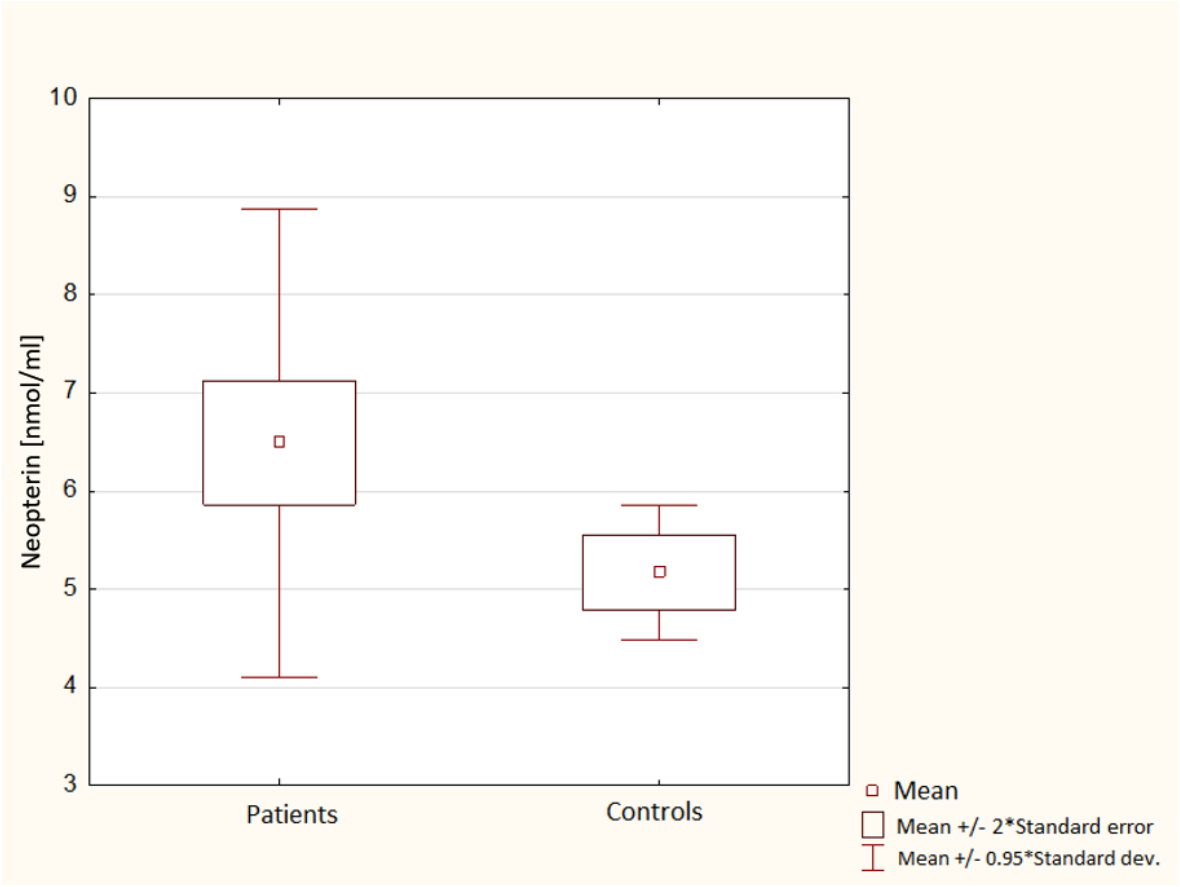

Figure 1. Mean neopterin concentration observed in patients and controls

sive patients. Avanzas et al. [17] assessed prognostic value of neopterin in the group of treated patients with hypertension, typical exertional chest pain and coronary artery stenosis of < 50% but without obstructive coronary artery disease, revealing that patients who developed adverse events during one year follow-up had significantly higher neopterin levels than patients without events (7.6 nmol/L vs. 5.4 nmol/L). Asci et al. [18] evaluated neopterin level in patients undergoing hemodialysis. The control group of that study consisted of three subgroups: healthy, diabetic and hypertensive subjects. Hypertensive control group had significantly higher serum neopterin level (16 +/- 1 nmol/L) than healthy control group (11 +/- 1 nmol/L). A recent study of Wang et al. [19] showed that plasma neopterin and hsCRP levels were increased in hypertensive patients with obstructive sleep apnea syndrome (OSAS) and correlated with severity of OSAS.

A similar tendency has been observed in our study: neopterin concentration was higher in hypertensive patients than in healthy controls (6.89 +/- 2.793 vs. 5.08 +/- 0.438); this result is consistent with the hypothesis on the role of inflammation processes in hypertension.

It should be also noted that assessed neopterin level seems to fall within the normal range, which is considered 8.7 nmol/L for 95th percentile of healthy population, according to Werner et al. [20]. However, it is usually recommended to estimate neopterin referential values for each study as they can differ significantly due to measurement method or population diversity.

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Conflict of interest statement
The authors declare that there is no conflict of interest in the authorship or publication of contribution.

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