THE NEW ARMENIAN MEDICAL JOURNAL
Vol.10 (2016), No 2, p. 44-53

Clinical Medicine

ENDOTHELIAL AND METABOLIC DISORDERS IN PATIENTS WITH HYPERTENSION ASSOCIATED WITH OBESITY AND HYPERURICEMIA

Molodan D.V.

Department of Therapy, Kharkiv National Medical University, Kharkiv, Ukraine

Received 18/10/2015; accepted for printing 24/03/2016

Abstract

The occurrence of such pathological conditions as hypertension and obesity are closely related to the metabolic, neurohormonal and hemodynamic disturbances affecting the state of endothelium. The influence of hyperuricemia on endothelial function in these patients is understudied, particularly in combination with other metabolic changes.

The aim of the study was to investigate endothelial function and metabolic abnormalities in patients with hypertension associated with obesity in the presence of hyperuricemia.

Totally 108 patients (52 (40%) males, 78 (60%) females) with hypertension of I and II stage, 1-3 degree of blood pressure increase and with obesity of I-II degree were examined during the study. The mean age of the examined patients was 58.0±0.6 years. All patients were divided into two groups depending on the level of hyperuricemia: patients with normouricemia (n=46) and patients with asymptomatic hyperuricemia (n=62). Control group was consisted of 12 practically healthy normotensive patients matched by sex and age with patients of the main group.

Endothelium-dependent vasodilatation was significantly reduced in patients with normouricemia and asymptomatic hyperuricemia in comparison with control group, the level of nitric oxide metabolites (NO_2+NO_3) was increased in the main group compared to the control group. The study of microalbuminuria and asymmetric dimethylarginine indicated the increase of these indices in hypertensive patients with obesity; particularly they were the highest in patients with asymptomatic hyperuricemia. Development of combined dyslipidemia and hyperinsulinism was identified in hypertensive patients with obesity, more pronounced in patients with high levels of uric acid in blood. Deterioration of purine metabolism, lipids and carbohydrates causes an adverse effect on the state of endothelium. Taking into account the correlation between endothelium-dependent vasodilatation and uric acid it can be assumed, that uric acid has a damaging effect on endothelium.

Endothelial dysfunction was noted in patients with essential hypertension associated with obesity, resulting in the decrease of endothelium-dependent vasodilatation, increase of the level of nitric oxide metabolites, asymmetric dimethylarginine and microalbuminuria. The deterioration of endothelial function was more expressed in patients with asymptomatic hyperuricemia. In multiple regression analysis it was revealed that changes of endothelium-dependent vasodilatation largely depend on such factors as uric acid, low-density lipoproteins, high-density lipoproteins, glucose, body mass index

Keywords: *endothelial dysfunction, hypertension, obesity, hyperuricemia.*

Introduction

Multiple studies conducted over the last few decades showed that vascular endothelium is actively involved in the regulation of vascular tone and vascular hemostasis and is a paracrine, endocrine and autocrine organ. Studies of endothelium condition suggest that the occurrence of endothelial dysfunction is the first important step in the development of atherosclerosis and formation of atherosclerotic lesions [*Anderson T et al., 1995; Kinlay S, Ganz P, 1997; Hadi H et al., 2005*]. In case of endothelial dysfunction de-

Address for Correspondence:
Kharkiv National Medical University
4 Nauky Avenue, Kharkiv 61022, Ukraine
Tel.: +38 (050) 266 68 35
E-mail: molvla@narod.ru

velopment the synthesis and bioavailability of vasodilators, particularly, nitric oxide (NO) decreases. Together with the reduction of endothelial nitric oxide production may be more sensitive to vasopressors or increase their synthesis [*Lerman A, Burnett J Jr, 1992*]. With the damage to the endothelium all of its functions change, the activity of the synthesis of pro-inflammatory factors, proliferation and coagulation factors increase, which is an important link in the formation of vascular disease [*Anderson T, 1999; Münzel T et al., 2005; Esper R et al., 2006*].

Among the diseases that lead to the development of endothelial dysfunction, the essential hypertension and obesity should be indicated [*Sato Y, 2001; Barton M, 2010; Shimbo D et al., 2010*]. The occurrence of these pathological conditions is associated with the formation of metabolic, hemodynamic and neurohormonal disorders affecting the condition of the endothelium [*Sturm W et al., 2009; Kobayasi R et al., 2010; Lobato N et al., 2012*]. In arterial hypertension the increase in blood pressure causes development of endothelium zone affection that eventually leads to its damage [*Rossoni L et al., 2002; Jurva J et al., 2006*]. Furthermore, different kinds of metabolic disorders are often identified in hypertensive patients, such as disorders of lipid, carbohydrate metabolism, and hyperuricemia are the most characteristic [*Heinig M, Johnson R, 2006; Grassi D et al., 2013*]. It was revealed, that adipocytes increase the production of pro-inflammatory factors that cause endothelial damage in case of obesity, especially its abdominal variant. Along with this, the activity of renin-angiotensin-aldosterone system is increased, and dyslipidemia, hyperinsulinemia and insulin resistance are developed [*Barbato J, Tzeng E, 2004; Spieker L et al., 2006; Batalova A et al., 2008*]. The role of such factor as hyperuricemia should be detailed. It is known that increased levels of uric acid in blood can lead to the development of such diseases as gout and urolithiasis. In addition, hyperuricemia is often detected in patients with metabolic disorders (so-called metabolic syndrome) [*Patterson R et al., 1998; Rossoni L et al., 2002; Mangge H et al., 2013*]. A series of studies showed the negative effect of the increase of uric acid indices on prognosis of patients with somatic diseases [*Anker S et al., 2003; Poudel B et al., 2012*]. There are a number of studies that indicate the important physiological significance of uric acid. It is established, that uric acid is a powerful antioxidant, moderate neurostimulator and neuroprotectant [*Waring W, 2002; Rudichenko V, 2010*].

Summarizing the facts, it can be assumed that the development of such diseases as essential hypertension and obesity is accompanied by the formation of endothelial dysfunction and metabolic disorders [*Montero D et al., 2012*]. The effect of dyslipidemia and disorders of carbohydrate metabolism on endothelial function is described [*Saad M et al., 2004; Jonk A et al., 2007*]. However, the role of uric acid and its effect on the endothelium are less studied, especially in combination with other metabolic disorders. Considering the abovementioned, a study of endothelial function and metabolic disorders was performed in patients with hypertension combined with obesity and hyperuricemia.

Material and methods

The study was performed on 108 patients with hypertension of I and II stage, 1-3 degree of blood pressure increase with accompanying obesity of I-II degree. Mean age of the examined patients was 58.0±0.6 years, among which the number of males was 52 (40%), females – 78 (60%). All patients were divided into two groups according to the level of hyperuricemia: I group included patients with normouricemia (n=46), II group – patients with asymptomatic hyperuricemia (n=62). Control group was consisted of 12 almost healthy normotensive patients matched by sex and age with patients of the main group. The study was performed in the hospital and clinics of SI "National Institute of Therapy named after L.T. Malaya of NAMS of Ukraine", which is the base of the Department of Internal Medicine No 1 of KNMU.

Selection of patients was conducted according to the modified criteria of Adult Treatment Panel III (2005) approved in European Guidelines in the treatment of hypertension (2007) and recommended by Ukrainian Association of Cardiologists of prevention and treatment of hypertension (2008). Indicators of normal levels of uric acid were established in accordance with the recommendations of European Antirheumatic League in

diagnosis and treatment of gout (2006). The upper limit of normal levels of uric acid had gender differences; its value in men was 420 *mcmol/l*, in women – 360 *mcmol/l*.

Patients with symptomatic hypertension, diabetes, inflammatory activity, coronary heart disease, heart failure of high functional class (III-IV according to New York Heart Association), gout, diseases of kidneys, liver, blood, alcohol abusers and mental diseases weren't included in the study during patient selection.\

Patients underwent common clinical, laboratory and instrumental examinations. Blood pressure level was determined as the average of three measurements conducted with intervals of 5 minutes in a sitting position. The assessment of anthropometric indices was carried out: height, weight, waist circumference. The body mass index was measured using the formula:

$$BMI=\frac{BW}{H}$$

where BMI – body mass index, BW – body weight (*kg*), H – height (m^2). Obesity was diagnosed when body mass index was >30.0 kg/m^2. The waist circumference was measured for verification of abdominal obesity, the rate was considered high if it was greater than 94 *cm* in men and 80 *cm* in women.

The determination of endothelium-dependent vasodilatation, metabolites of nitric oxide (NO2+NO3), microalbuminuria and the inhibitor of nitric oxide synthase substrate – asymmetric dimethylarginine was conducted to study the function of the endothelium [*Böger R, 2006*].

Endothelium-dependent vasodilatation was assessed by cuff test with reactive hyperemia [*Celermajer D et al., 1992*]. The study was conducted by Vivid 3 ultrasonic diagnostic complex (General Electric, USA); the sensor with a frequency of 7.5 *MHz* was used for scanning of the brachial artery. Evidence of endothelial dysfunction was the decrease of endothelium-dependent vasodilatation after decompression of the brachial artery. Vasodilatation of less than 10% was considered diagnostically significant.

The determination of glucose, uric acid and lipid profile of blood was performed by immunoenzymometric method on a photometer analyzer "Humareader No 2106" (Human GmbH, Germany). The levels of total cholesterol, triglyceride, cholesterol of low-density lipoprotein and high-density lipoprotein were studied. Atherogenic coefficient was calculated by the following formula:

$$AC=\frac{TC-HDL}{HDL}$$

where AC – atherogenic coefficient, TC – total cholesterol, HDL – high-density lipoprotein. Fasting insulin levels were determined in serum by ELISA using a kit "DRG" (Germany). Increase of insulin level (>12.5 *mU/ml*) indicated the hyperinsulinemia. Homeostasis model assessment of insulin resistance was used to determine insulin resistance, which was calculated by the formula:

$$HOMA=\frac{FG \times FI}{22.5}$$

where HOMA – homeostasis model assessment of insulin resistance, FG – fasting glucose, FI – fasting insulin. The index value >2.77 indicated the insulin resistance.

Research of asymmetric dimethylarginine levels was done using kit of "Immunodiagnostika" firm (Germany); microalbuminuria was done using kit of "Granum" (Ukraine). Amount of stable metabolites of nitric oxide (NO2 and NO3) in the serum was investigated by spectrophotometrical method using the Griess reagent (Austria) [*Kiselik I et al., 2001; Orlova E, 2002*].

Statistical processing of the results was performed using the IBM SPSS Statistics software package, version 20.0. Quantitative characteristics are presented as M ± m (M - arithmetic mean, m - mean error of the arithmetic mean). In the vast majority of cases the obtained results did not obey the laws of normal distribution; therefore, non-parametric methods were used to assess the significance of differences in the results (Mann-Whitney U test to check the hypothesis about the equality of two mean independent samples). Spearman rank correlation coefficient was calculated to evaluate the correlations. Differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

Obtained study results showed that patients of main and control groups were matched by sex and age. While comparing the values of body mass index and blood pressure levels it was found that in hypertensive patients with obesity (both with normouricemia and asymptomatic hyperurice-

mia), these indices are higher than in the control group ($p<0.05$). Whereby, the numbers of systolic blood pressure was significantly higher in patients of II group compared to patients of I group ($p<0.05$) (Table 1).

The assessment of endothelial function showed that endothelial function is reduced in patients of the main group with normal and increased uric acid levels, as evidenced by the reduction of endothelium-dependent vasodilatation, increase of metabolites of nitric oxide, microalbuminuria and asymmetric dimethylarginine (Table 2).

Thus, in patients of control group endothelium-dependent vasodilatation was 12.0±1.03%, in I group of patients – 5.43±1.19%, and in II group – 1.92±1.05%, the differences between groups were significant ($p<0.05$). The level of nitric oxide metabolites (NO2+NO3) in the control group was 21.59±5.86 *mcmol/l,* in I group – 31.75±5.16 *mcmol/l,* and in II group – 42.11±14.98 ($p<0.05$). The study of microalbuminuria and asymmetric dimethylarginine testifies to the increase of the level of these parameters in hypertensive patients with obesity. Their level was higher in patients with asymptomatic hyperuricemia. Thus, the value of microalbuminuria in the control group was 8.25±4.49 *mg*/day, asymmetric dimethylarginine – 0.34±0.05 *mcmol/l*, microalbuminuria was 18.28±7.72 *mg*/day in patients with normouricemia, asymmetric dimethylarginine – 0.64±0.08 *mcmol/l*, and in patients with asymptomatic hyperuricemia, the value of levels were 29.6±13.87 *mg*/day and 0.75±0.12 *mcmol/l*, respectively ($p<0.05$). Therefore, with the growth of uric acid level the endothelial function was deteriorated.

Thus, in examined patients endothelium-dependent vasodilatation was decreased and metabolites of nitric oxide, asymmetric dimethylarginine and microalbuminuria were increased. Apparently, this dynamics of parameters was associated with the

Table 1.

Anthropometric indicators, levels of blood pressure and blood uric acid in hypertensive patients with obesity and in healthy individuals (M (m))

Indicators	Main group I (n=46)	Main group II (n=62)	Control group (n=12)
Sex (M/F)	20/26	24/38	5/7
Age, years	57.24±7.01	58.32±7.35	54.60±7.59
Systolic blood pressure (*mmHg*)	157.06±9.40*	166.53±6.78* **	114.95±5.511
Diastolic blood pressure (*mmHg*)	99.56±6.39*	100.88±7.21*	75.00±6.48
Body mass index (kg/m^2)	33.25±2.66*	36.64±3.76*	22.60±2.95
Uric acid (*mcmol/l*)	289.41±48.79*	481.32±66.97* **	254.05±39.27

Notes: ** – significance of differences in comparison with the control group ($p<0.05$), ** – significance of differences between patients of I and II groups ($p<0.05$).*

Table 2.

Indicators of endothelial function in hypertensive patients with obesity and in healthy individuals (M (m))

Indicators	Main group I (n=46)	Main group II (n=62)	Control group (n=12)
Endothelium-dependent vasodilatation (%)	5.43±1.19*	1.92±1.05*.**	12.0±1.03
Metabolites of nitric oxide (*mcmol/l*)	31.75±5.16*	42.11±14.98*.**	21.59±5.86
Microalbuminuria (*mg*/day)	18.28±7.72*	29.6±13.87*.**	8.25±4.49
Asymmetric dimethylarginine (*mcmol/l*)	0.64±0.08*	0.75±0.12*.**	0.34±0.05

Notes: ** – significance of differences in comparison with the control group ($p<0.05$), ** – significance of differences between patients of I and II groups ($p<0.05$).*

damage of endothelium and decrease of vasodilator synthesis, particularly, nitric oxide production by endothelial synthase [*Doshi S et al., 2001*]. Confirmation of decreased activity of endothelial nitric oxide synthase is the fact that the levels of competitive antagonist of nitric oxide synthase – asymmetric dimethylarginine, were increased. The increase of this factor is associated with a more rapid development of the atherosclerotic process and indicates an increase of the risk of vascular events [*Böger R et al., 1998; Miyazaki H et al., 1999*]. All these changes tend to occur on the base of the "low-level inflammation" of vascular endothelium. The results are the reduction in the activity of endothelial nitric oxide synthase and the increase of the activity of inducible nitric oxide synthase, accompanied by a significant increase of nitric oxide metabolites [*Vilchuk K, 2011*].

While analyzing the state of endothelium, some of integral indicators of its functions – endothelium-dependent vasodilatation and microalbuminuria were studied. It allowed to study not only the particular mechanisms of disruption of the endothelium, but also to evaluate its function as a whole [*Tebbe U et al., 2010*]. Dynamics of mentioned two indicators allowed confirming that there are obvious vascular lesions of systemic nature in patients with essential hypertension and obesity, and especially with the asymptomatic hyperuricemia, which testifies to an unfavorable course of the disease [*Wang J et al., 2001*]. It is proved by the fact that the increase of the microalbuminuria is closely linked not only with the function of the endothelium, but also with the development of hypertrophy and myocardial ischemia, thickening of the intima-media coefficient of carotid arteries, the development of insulin resistance and dyslipidemia (particularly hypercholesterolemia) [*Jensen J et al., 1995; Redon J et al., 1996; Potremoli R et al., 1998; Diercks G et al., 2000; Ivanov D, 2008*].

Thus, the obtained results suggest that the development of essential hypertension and obesity is accompanied by the deterioration of endothelial function. Moreover, the growth level of uric acid makes a contribution to this process, because the worst indicators of the state of endothelium were observed in patients with asymptomatic hyperuricemia and were worse than in patients with normal levels of uric acid and in patients of the control group.

Furthermore, in accordance with the purpose of the study, the status of lipid and carbohydrate metabolism was also studied. As a result, it was found that the development of combined dyslipidemia and hyperinsulinemia takes place in the group with essential hypertension and obesity, more obvious in patients with elevated levels of uric acid in blood (Table 3, 4).

While comparing the lipid metabolism in patients of I and II groups it was found that indicators were deteriorated with increasing concentrations of uric acid. Thus, in II group the values of total cholesterol, triglyceride, low-density lipoprotein were higher and high-density lipoprotein were lower. The differences in the values of triglyceride and cholesterol of high-density lipoprotein were statistically significant, which is a manifestation of combined dyslipidemia (Table 3).

During the study of carbohydrate metabolism an increase of insulin levels and HOMA index was

TABLE 3

Indicators of lipid metabolism in hypertensive patients with obesity and in healthy individuals (M (m))

Indicators		Mani group		Control group (n=12)
		I (n=46)	II (n=62)	
Atherogenic coefficient		3.46±0.69*	4.40±0.94*.**	1.74±0.36
Total cholesterol (*mmol/l*)		5.27±0.49*	5.49±0.54*	3.89±0.22
Triglyceride (*mmol/l*)		1.52±0.23*	1.91±0.60*.**	0.99±0.35
Lipoproteins	Low-density (*mmol/l*)	3.38±0.43*	3.60±0.52*	1.99±0.16
	High density (*mmol/l*)	1.19±0.16*	1.03±0.11*.**	1.44±0.24

Notes: ** – significance of differences in comparison with the control group ($p<0.05$), ** – significance of differences between patients of I and II groups ($p<0.05$).*

Table 4.

Indicators of carbohydrate metabolism in hypertensive patients with obesity and in healthy individuals (M (m))

Indicators	Main group		Control group
	I (n=46)	II (n=62)	(n=12)
Glucose (*mmol/l*)	4.78±0.42	4.73±0.59	4.71±0.35
Insulin (*mcIU/ml*)	13.73±9.06*	18.74±6.78*,**	1.95±1.80
Homeostasis assessment model (*y.e.*)	2.94±2.02*	4.04±1.73*,**	0.41±0.39

Notes: ** – significance of differences in comparison with the control group (p<0.05), ** – significance of differences between patients of I and II groups (p<0.05).*

noted in hypertensive patients with obesity. Differences between these parameters were statistically significant comparing with hypertensive patients and control subjects and in the comparison between I and II groups (p<0.05). Thus, in I group of patients insulin level was 13.73±9.06 *mkIU/ml*, the level of HOMA – 2.94±2.02 *y.e.*, and in II group of patients – 18.74±6.78 *mkIU/ml* and 4.04±1.73 y.*e.,* respectively (p<0.05). Such changes show the development of insulin resistance, along with progressive increase of uric acid.

Monitoring the state of endothelium, carbohydrate and lipid metabolism suggests that studied parameters in patients with essential hypertension and obesity were worse than in patients with asymptomatic hyperuricemia. A possible explanation for this may be the work in which it was shown that the development of hyperuricemia causes decrease of activity of nitric oxide synthase in endothelium and the same worsens its state [*Mazzali M et al., 2001; Khosla U et al., 2005*]. Decreased activity of endothelial nitric oxide synthase may also be one of the causes of more severe hypertension and cause progression of metabolic disorders. In one experimental study it was demonstrated that hypertension, hypercholesterolemia, hypertriglyceridemia were developed in mice deprived of nitric oxide synthase, and also insulin resistance was formed [*Cook S et al., 2003*]. In addition, in hyperuricemia, worsening of endothelial function could be due to increased synthesis of pro-inflammatory adipokines and decrease of activity of anti-inflammatory factors, which in turn enhances the inflammatory processes in the endothelium and can induce the development of metabolic disorders of carbohydrates and lipids [*Baldwin W et al., 2011*].

Analyzing changes in endothelial function, the correlation and its strength was examined between endothelium-dependent vasodilatation and the level of uric acid, and also between carbohydrate and lipid metabolism. It was found that the correlation between the level of uric acid and endothelium-dependent vasodilatation in hypertensive patients with obesity and asymptomatic hyperuricemia was r_s= -0.796; p<0.001, between endothelium-dependent vasodilatation and HOMA index – r_s= -0.506, p<0.001, with insulin level – r_s= -0.501, p<0.001, with glucose – r_s= -0.155, p>0.05, with the values of total cholesterol – r_s= -0.203, p>0.05, triglyceride – r_s= -0.056, p>0.05, low-density lipoprotein – r_s= -0.231, p>0.05, high-density lipoprotein – r_s= -0.056, p>0.05. By increasing the level of uric acid (hypertensive patients with obesity and asymptomatic hyperuricemia) its correlation with indicators of endothelium-dependent vasodilatation becomes more expressed (r_s= -0.860; p<0.001). Also in these patients correlation of endothelium-dependent vasodilatation with metabolic factors increased, the correlation between endothelium-dependent vasodilatation and HOMA index was r_s= -0.506, p<0.001, with insulin level – r_s= -0.501, p<0.001, with glucose – r_s= -0.155, p>0.05. Lipid metabolism indicators correlated with endothelium-dependent vasodilatation in such ways: total cholesterol – r_s= -0.203, p>0.05, triglyceride – r_s= -0.056, p>0.05, low-density lipoprotein – r_s= -0.231, p>0.05, high-density lipoprotein – r_s= -0.056, p>0.05.

Obtained results indicate that the deterioration of purine metabolism, lipids and carbohydrates in patients with asymptomatic hyperuricemia causes a more pronounced negative effect on the condi-

tion of the endothelium, and according to correlation between uric acid and endothelium-dependent vasodilatation it can be assumed that uric acid has a damaging effect on the endothelium. Linear multiple regression model was used to objectify the extent of this influence. The analysis showed that the indicators of uric acid, low-density lipoprotein, high-density lipoprotein, glucose and body mass index were the most "important" in patients with hypertension associated with obesity and hyperuricemia, the regression coefficient was set for each of them. If the coefficient was positive its growth led to the increase of endothelium-dependent vasodilatation, if coefficient was negative, its increase led to the decrease of vasodilatation. As the table shows, all parameters included in the analysis were highly statistically significant ($p<0.05$). The patterns were identified; this allowed constructing a regression equation, which has the following form:

EDVD = 11.547 - 0.015 **UA** - 1.528 **LDL** +
+2.330 **HDL+** + 0.893 **Gl** – 0.097 **BMI**,

where UA – uric acid, LDL – low-density lipoprotein, HDL – high-density lipoprotein, Gl - glucose, BMI – body mass index.

It should be noted that in recent years there have been many studies showing how non-invasive study of endothelial function may provide important information for the assessment of individual risk, prognosis of the patient and the effectiveness of therapy (in addition to the methods that are already known for their informative: Scale SCORE and Framingham) [*Flammer A et al., 2012*]. The use of noninvasive determination of endothelial function is also important because it is safe for the patient and highly informative. According to some experts, the endothelium can be considered as a factor that objectively reflects the state of the cardiovascular system. In this regard, it can be assumed that the presented equation will be useful for application in clinical practice, as it allows assessing the condition of the endothelium and to implement its monitoring during the treatment.

Thus, the study established that endothelial dysfunction is noted in patients with hypertension associated with obesity that manifests in the reduction of endothelium-dependent vasodilatation, increase of the level of nitric oxide metabolites, asymmetric dimethylarginine and microalbuminuria.

Deterioration of endothelial function occurred with increasing levels of uric acid, and was greater in patients with hyperuricemia while comparing the patients of control group and patients with essential hypertension and normal parameters of uric acid.

The study found a disorder of lipid metabolism with the development of combined dyslipidemia (increase of the levels of total cholesterol, cholesterol of low-density lipoprotein, triglyceride and decrease of cholesterol of high-density lipoprotein) and the deterioration of carbohydrate metabolism with the development of hyperinsulinemia and increased HOMA index. These changes were most expressed in patients with hyperuricemia.

A close correlation between the level of uric acid and indicators of endothelial function (endothelium-dependent vasodilatation (r_s= -0.860; $p<0.001$), nitric oxide metabolites (r_s= 0.830; $p<0.001$), asymmetric dimethylarginine (r_s= 0.831; $p<0.001$), microalbuminuria (r_s= 0.852; $p<0.001$) was revealed. In multiple regression analysis, it was established that changes of endothelium-dependent vasodilatation largely depend on such parameters as: uric acid, low-density lipoprotein, high- density lipoprotein, glucose, body mass index.

REFERENCES

1. *Anderson TJ, Gerhard MD, Meredith IT, Charbonneau F, Delagrange D., et al.* Systemic nature of endothelial dysfunction in atherosclerosis. Am J Cardiol. 1995; 75(6): 71B-74B.
2. *Anderson TJ.* Assessment and treatment of endothelial dysfunction in humans. J Am Coll Cardiol. 1999; 34(3): 631-638.
3. *Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D., et al.* Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003; 107(15): 1991-1997.
4. *Baldwin W, McRae S, Marek G, Wymer D, Pannu V., et al.* Hyperuricemia as a mediator

of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. Diabetes. 2011; 60(4): 1258-1269.

5. *Barbato JE, Tzeng E.* Nitric oxide and arterial disease. J Vasc Surg. 2004; 40(1): 187-193.
6. *Barton M.* Obesity and aging: determinants of endothelial cell dysfunction and atherosclerosis. Pflugers Arch. 2010; 460(5): 825-837.
7. *Batalova AA, Khovaeva YaB, Berg MD.* [Stages violation of endothelial function in the development of hypertension and atherosclerosis] [Published in Russian]. Cardiovascular therapy and prevention: materials of Russian national Congress of Cardiologists. App. 1. 2008; 7(6): 44.
8. *Böger RH, Bode-Böger SM, Szuba A, Tsao PS, Chan JR., et al.* ADMA: a novel risk factor for endothelial dysfunction: its role in hypercholesterolemia. Circulation. 1998; 98(18): 1842-1847.
9. *Böger RH.* Asymmetric dimethylarginine (ADMA): a novel risk marker in cardiovascular medicine and beyond. Ann Med. 2006; 38(2): 126-136.
10. *Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI., et al.* Non-invasive detection of endothelial disfunction in children and adults at risk of atherosclerosis. Lancet. 1992; 340(8828): 1111-1115.
11. *Cook S, Hugli O, Egli M, Vollenweider P, Burcelin R., et al.* Clustering of cardiovascular risk factors mimicking the human metabolic syndrome X in eNOS null mice. Swiss Med Wkly. 2003; 133(25-26): 360-363.
12. *Diercks GF, van Boven AJ, Hillege HL, Janssen WM, Kors JA., et al.* Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large non-diabetic population. The PREVEND (Prevention of Renal and Vascular Endstage Disease) study. Eur Heart J. 2000; 21(23): 1922-1927.
13. *Doshi SN, Naka KK, Payne N, Jones CJ, Ashton M., et al*. Flow-mediated dilatation following wrist and upper arm occlusion in humans: the contribution of nitric oxide. Clin Sci (Lond). 2001; 101(6): 629-635.
14. *Esper RJ, Nordaby RA, Vilariño JO, Paragano A, Cacharrón JL, Machado RA*. Endothelial dysfunction: a comprehensive appraisal. Cardiovasc Diabetol. 2006; 5:4.
15. *Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J., et al.* The assessment of endothelial function: from research into clinical practice. Circulation. 2012; 126(6): 753-767.
16. *Grassi D, Ferri L, Desideri G, Di Giosia P, Cheli P., et al.* Chronic hyperuricemia, uric acid deposit and cardiovascular risk. Curr Pharm Des. 2013; 19(13): 2432-2438.
17. *Hadi HA, Carr CS, Al Suwaidi J.* Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag. 2005; 1(3): 183-198.
18. *Heinig M, Johnson RJ.* Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve Clin J Med. 2006; 73(12): 1059-1064.
19. *Ivanov DD.* [Microalbuminuria: a look of neurologist] [Published in Ukrainian]. Health of Ukraine. 2008; 21(1): 18-19.
20. *Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B.* Microalbuminuria reflects generalized transvascular albumin leakiness in clinically healthy subject. Clin Sci (Lond). 1995; 88(6): 629-633.
21. *Jonk AM, Houben AJ, de Jongh RT, Serné EH, Schaper NC, Stehouwer CD*. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology (Bethesda). 2007; 22: 252-260.
22. *Jurva JW, Phillips SA, Syed AQ, Syed AY, Pitt S, Weaver A, Gutterman DD.* The effect of exertional hypertension evoked by weight lifting on vascular endothelial function. J Am Coll Cardiol. 2006; 48(3): 588-589.
23. *Khosla UM, Zharikov S, Finch JL, Nakagawa T,*

Roncal C., et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005; 67(5): 1739-1742.

24. *Kinlay S, Ganz P.* Role of endothelial dysfunction in coronary artery disease and implications for therapy. Am J Cardiol. 1997; 80(9A): 11I-16I.

25. *Kiselik IO, Lutsyk MD, Shevchenko LYu.* [Specifics of determining nitrite and nitrate in blood of patients with viral hepatitis and jaundice another etiology] [Published in Ukrainian]. Laboratory Diagnostics. 2001; 3: 43-45.

26. *Kobayasi R, Akamine EH, Davel AP, Rodrigues MA, Carvalho CR, Rossoni LV.* Oxidative stress and inflammatory mediators contribute to endothelial dysfunction in high-fat diet-induced obesity in mice. J Hypertens. 2010; 28(10): 2111-2119.

27. *Lerman A, Burnett JC Jr.* Intact and altered endothelium in regulation of vasomotion. Circulation. 1992; 86(6): III12-19.

28. *Lobato NS, Filgueira FP, Akamine EH, Tostes RC, Carvalho MH, Fortes ZB*. Mechanisms of endothelial dysfunction in obesity-associated hypertension. Braz J Med Biol Res. 2012; 45(5): 392-400.

29. *Mangge H, Zelzer S, Puerstner P, Schnedl WJ, Reeves G*. Uric acid best predicts metabolically unhealthy obesity with increased cardiovascular risk in youth and adults. Obesity (Silver Spring). 2013; 21(1): E71-77.

30. *Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH., et al.* Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001; 38(5): 1101-1106.

31. *Miyazaki H, Matsuoka H, Cooke JP, Usui M, Ueda S, Okuda S, Imaizumi T.* Endogenous nitric oxide synthase inhibitor: a novel marker of atherosclerosis. Circulation. 1999; 99(9): 1141-1146.

32. *Montero D, Walther G, Perez-Martin A, Roche E, Vinet A.* Endothelial dysfunction, inflammation, and oxidative stress in obese children and adolescents: markers and effect of lifestyle intervention. Obes Rev. 2012; 13(5): 441-455.

33. *Münzel T, Daiber A, Ullrich V, Mülsch A.* Vascular consequences of endothelial nitric oxide synthase uncoupling for the activity and expression of the soluble guanylyl cyclase and the cGMP-dependent protein kinase. Arterioscler Thromb Vasc Biol. 2005; 25(8): 1551-1557.

34. *Orlova EA.* [Analysis of nitrites and nitrates in the tissue in experimental acute renal failure] [Published in Ukrainian]. Ukrainskiy zhurnal ekstremal'noy meditsiny. 2002; 3(1): 79-82.

35. *Patterson RA, Horsley ET, Leake DS.* Prooxidant and antioxidant properties of human serum ultrafiltrates toward LDL: important role of uric acid. J Lipid Res. 2003; 44(3): 512-521.

36. *Potremoli R, Nicolella C, Viazzi F, Ravera M, Sofia A., et al.* Microalbuminuria in an early marker of target organ damage in essential hypertension. Am J Hypertens. 1998; 11(4 Pt 1): 430-438.

37. *Poudel B, Yadav BK, Nepal AK, Jha B, Raut KB.* Prevalence and association of microalbuminuria in essential hypertensive patients. N Am J Med Sci. 2012; 4(8): 331-335.

38. *Redon J, Baldo E, Lurbe E, Bertolin V, Lozano JV., et al.* Microalbuminuria, left ventricular mass and ambulatory blood pressure in essential hypertension. Kidney Int Suppl. 1996; 55: S81-84.

39. *Rossoni LV, Salaices M, Miguel M, Briones AM, Barker LA., et al*. Ouabain-induced hypertension is accompanied by increases in endothelial vasodilator factors. Am J Physiol Heart Circ Physiol. 2002; 283(5): H2110-2118.

40. *Rudichenko VM.* [Hyperuricemia, gout and hypertension – clinical and experimental parallels in important activities of general practitioner (family medicine)] [Published in Ukrainian]. Arterial hypertension. 2010; 4: 72-81.

41. *Saad MF, Rewers M, Selby J, Howard G, Jinagouda S., et al.* Insulin resistance and hypertension: the Insulin Resistance Atherosclerosis study. Hypertension. 2004; 43(6): 1324-1331.

42. *Sato Y.* Current understanding of the biology of vascular endothelium. Cell Struct Funct. 2001; 26(1): 9-10.

43. *Shimbo D, Muntner P, Mann D, Viera AJ, Homma S., et al.* Endothelial dysfunction and the risk of hypertension: the multi-ethnic study of atherosclerosis. Hypertension. 2010; 55(5): 1210-1216.

44. *Spieker LE, Flammer AJ, Lüscher TF.* The vascular endothelium in hypertension. Handb Exp Pharmacol. 2006; 176(2): 249-283.

45. *Sturm W, Sandhofer A, Engl J, Laimer M, Molnar C., et al*. Influence of visceral obesity and liver fat on vascular structure and function in obese subjects. Obesity (Silver Spring). 2009; 17(9): 1783-1788.

46. *Tebbe U, Bramlage P, Lüders S, Cuneo A, Sistig P., et al.* Follow-up of cardiovascular risk markers in hypertensive patients treated with irbesartan: results of the i-SEARCH Plus Registry. J Clin Hypertens (Greenwich). 2010; 12(12): 909-916.

47. *Vilchuk KU.* [Determining of the role of endothelium and macrophage nitric oxide at the mechanisms of the development of pyelonephritis in children] [Published in Belarusian]. Biotekhnologiya. 2011; 4: 42-45.

48. *Wang JG, Staessen JA, Fagard RH, Birkenhäger WH, Gong L, Liu L.* Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. Hypertension. 2001; 37(4): 1069-1074.

49. *Waring WS.* Uric acid: an important antioxidant in acute ischemic stroke. QJM. 2002; 95(10): 691-693.