



CLINICAL CASE

**BOLTON TOOTH SIZE DISCREPANCIES  
IN DIFFERENT MALOCCLUSIONS**

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**ABSTRACT**

*Inadequacy between maxillary and mandibular teeth sizes can pose problems in achieving ideal occlusion on finishing stage of orthodontic treatment. Bolton analysis is one of the most popular methods for determining tooth size abnormality.*

*The aim of investigation was to determine overall and anterior Bolton ratios in individuals living in Armenia with different malocclusions (Angle Class I, II, and III) and to compare them with Bolton's norm. Experimental material comprised 80 pre-treatment study casts, selected from the models of orthodontic patients aged 12-25 and was divided into 4 groups. First group included study casts of patients with malocclusions of Class I (n=20), second group – with malocclusions of Class II, division 1 (n=20), third group – Class II, division 2 (n=20) and fourth group – Class III (n=20).*

*Statistical analysis of the data was conducted using SPSS. While comparing the mean overall ratio with the original Bolton norm, statistically significant differences were found in patients with malocclusions of Class II, 2, and while comparing mean anterior ratio – in patients with malocclusions of Class I, Class II, 1 and Class II, 2. Overall ratio discrepancies with the norm were found in 11.25% of studied population, exceeding 2 standard deviations, while anterior ratio discrepancies were 28.75%.*

*The result of the present study showed that a large number of orthodontic patients in Armenia have Bolton tooth size discrepancy exceeding 2 standard deviations. Therefore, Bolton's ratios in all orthodontic patients and especially in patients with malocclusions of Class III must be determined before the treatment.*

**KEYWORDS:** Bolton analysis, Bolton ratios, tooth-size discrepancy, malocclusion.

**INTRODUCTION**

A tooth-size discrepancy has been described as a relative excess of tooth structure in one arch in relation to the other one [Fields H, 1981]. It also can be defined as a disproportion of individual tooth sizes. Approximately 5% of population has some degree of discrepancies of individual tooth sizes [Proffit W et al., 2007]. The tooth size must be in harmony with the arch size to ensure proper alignment, overbite, overjet and to achieve a good occlusal interdigitation of the dentition. As the patient with interarch tooth size discrepancies re-

quires either removal (interproximal stripping) or addition (composite buildups or porcelain veneers) of tooth structure to open or close spaces in the opposite arch, it is important to determine the amount and location of a tooth size discrepancy before starting the treatment. Many authors studied tooth width as well as its relation to occlusion [Black G, 1902; Ballard M, 1944; Neff C, 1949; Steadman S, 1952; Lundstrom A, 1954].

Bolton analysis is one of the most popular methods for determining tooth-size discrepancy. According to his assumptions, proper occlusal interdigitation or coordination of arches in the finishing stage of orthodontic treatment would be difficult without proper mesio-distal tooth size ratio between maxillary and mandibular teeth. Bolton

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performed analysis on 55 patients with excellent occlusion, including 44 orthodontically treated (non-extraction) and 11 untreated subjects and suggested 2 indices [Bolton W, 1958]. The overall Bolton ratio is the percentage ratio obtained by summing the width of 12 mandibular and 12 mandibular teeth, composing  $91.3 \pm 1.91\%$ , and anterior ratio – percentage ratio obtained by summing the width of 6 mandibular and 6 maxillary teeth, composing  $77.2 \pm 1.65\%$ . If the patient presents with Bolton discrepancies, it is necessary to compensate for this discrepancy by slenderization of the dental arch or space opening and performing restoration. The localization of tooth-size discrepancy has to be found in cases, if:

- Bolton overall ratio shows an excess on maxillary arch of 4 mm, and anterior ratio also shows 4 mm excess, than the venue of slicing is the upper frontal segment (cuspid-to-cuspid).
- Overall ratio shows an excess on maxillary arch of 4 mm, and anterior ratio is normal, than the venue of slicing is the upper lateral segment (premolars and bicuspid).
- Overall ratio shows an excess on maxillary arch of 4 mm, and anterior ratio also shows 2 mm excess, than the venue of slicing should occur is the whole upper dental arch.

In 1962, U.A. Bolton had expanded his study on the clinical application of his tooth size analysis, where he suggested a different overall ratio for premolar extraction cases. The overall ratio was in a range from 87 to 89% with the mean value of 88% in patients who didn't have tooth size discrepancy after extraction of four premolars. Many authors in their studies had tried to determine whether the extraction of 4 premolars as a requirement of orthodontic therapy is a factor in the creation of tooth-size discrepancy [Saatci P, Yukay F, 1997; Tong H et al., 2004]. Pre-treatment mesio-distal dimensions of mandibular and maxillary teeth were measured, recorded on a computer program and subjected to Bolton's analysis. Then they performed hypothetical tooth extraction of all premolar combinations by computer on each patient. The obtained results confirmed Bolton's conclusion, that the removal of the larger mandibular second premolars often improves the overall ratio [Bolton W, 1962].

Bolton ratio allows the orthodontist to gain insight into the functional and esthetic outcome of a

given case without the use of a diagnostic setup. The aim of the present investigation was to calculate the overall and anterior ratios in patients with malocclusions of Class I, II, III living and to compare them with standards suggested by Bolton.

#### MATERIAL AND METHODS

The study was conducted on 80 pre-treatment study casts, selected from models of patients, living in Armenia, who applied for orthodontic treatment to the University stomatological clinics N2 of YSMU, Children stomatological center after E. Mnacakanyan and Alfa-Stom private orthodontic clinic.

The following inclusion criteria were used in the selection of study models:

- patients' age from 12 to 25 years
- presence of good quality diagnostic models
- fully erupted permanent dentition from the first molar to the first molar of the opposite side in both arches
- absence of interproximal caries, restorations, prosthetic crowns and bridges
- no extraction or interproximal stripping performed
- no obvious interproximal or occlusal teeth wear.

Diagnostic models were divided into 4 groups. First group included study casts of patients with malocclusions of Class I (n=20), second group – with malocclusions of Class II, division 1 (n=20), third group – Class II, division 2 (n=20) and fourth group – Class III (n=20). All measurements on the study models were undertaken by the resident of the Department of children stomatology and orthodontics of YSMU. The mesiodistal tooth sizes were measured directly on the study models using digital calipers accurate to 0.01 mm. The width of each tooth was measured from its mesial contact point to its distal contact point at its greatest interproximal distance. The points on the approximate surfaces were defined as contact points, which should be touching when the teeth were perfectly aligned [Jensen E et al., 1957]. The sum of the widths of the 12 mandibular and 12 maxillary teeth as well as the sum of the widths of the 6 mandibular and 6 maxillary teeth was calculated for each pair of study casts. Overall and anterior Bolton's ratios were calculated and compared with original Bolton norm. Statistical analysis of the data was conducted using SPSS.

**RESULTS AND DISCUSSION**

Indicators of overall and anterior Bolton's ratios for all groups with malocclusions are shown in Table 1.

The results for overall and anterior Bolton ratios in each individual group with malocclusion are presented in Table 2.

Frequency indices of tooth size discrepancies, exceeding 2 standard deviations by Bolton, are presented in Table 3.

Present study revealed, that the mean overall ratio was 91.6%, and mean anterior ratio – 79.1%. These ratios statistically significantly differ from Bolton's norm.

Comparing overall ratio in the individual malocclusion groups with Bolton's norm statistically significant differences were found for the Class II,

**TABLE 1.**

Indicators of overall and anterior ratios for all study groups (n=20)

Class I		Class II,1		Class II,2		Class III	
OR	AR	OR	AR	OR	AR	OR	AR
91.7	81.7	96.3	85.3	91.6	79.9	96.6	84.8
94.07	79.9	92.5	80.9	97.6	81.2	95.3	83.7
92.6	79.2	90.8	76.4	93.3	76.2	92.3	77.4
92.1	82.7	92.7	77.7	93.6	82.1	92.9	81.6
89.8	79.2	91.7	79.2	92.0	78.4	91.3	77.8
93.1	79.4	94.4	80.0	91.9	81.2	94.2	79.3
91.5	77.2	90.6	81.3	91.2	80.4	94.1	79.6
90.7	75.7	95.0	81.8	90.3	78.1	88.9	74.7
91.4	78.1	92.4	81.7	92.8	82.4	85.5	73.4
89.5	78.4	94.5	78.1	93.2	79.4	88.7	76.3
92.6	78.2	86.5	78.3	90.9	78.5	92.2	82.5
92.0	78.9	90.9	75.4	90.4	77.6	88.9	75.0
91.9	77.1	91.2	75.7	87.8	77.2	95.4	82.4
91.3	79.9	91.0	80.1	92.8	77.9	99.2	88.4
88.2	75.9	93.0	78.8	93.1	80.3	91.8	66.4
91.1	78.4	93.4	80.0	91.6	78.6	92.8	77.9
92.6	77.4	94.7	79.5	93.5	82.1	92.6	77.8
87.7	80.3	92.9	79.3	89.5	75.2	91.9	75.0
91.0	78.0	89.3	74.8	100.1	86.1	93.2	80.5
91.2	79.2	91.9	77.2	95.3	83.9	91.7	78.9

NOTES: OR- overall ratio, AR-anterior ratio (see explanation in the text).

**TABLE 2.**

Significance of overall and anterior Bolton ratios

Malocclusion	Sample size	Min.	Max.	Mean	SD	p
Class I	OR	20	87.7	94.1	91.30	1.55 NS
	AR	20	75.7	82.7	78.4	1.72 **
Class II.1	OR	20	86.5	96.3	92.28	2.22 NS
	AR	20	74.8	85.3	79.07	2.53 **
Class II.2	OR	20	87.8	100.1	92.62	2.71 *
	AR	20	75.2	86.1	79.83	2.67 ***
Class III	OR	20	85.5	99.2	92.47	3.04 NS
	AR	20	66.4	88.4	78.67	4.75 NS

NOTE: \* – p<0.05, \*\* – p<0.01, \*\*\* – p<0.001, NS-Not significant, OR- overall ratio, AR-anterior ratio (see explanation in the text).

**TABLE 3.**

Frequency of Bolton tooth size discrepancies exceeding 2 standard deviations

Malocclusion	N	SD	%
Class I	OR	0	+2SD
	AR	2	+2SD 10
Class II,1	OR	1	+2SD 5
	AR	5	+2SD 25
Class II,2	OR	3	+2SD 15
	AR	7	+2SD 35
Class III	OR	4	+2SD 25
		1	-2SD
	AR	7	+2SD 45
		2	-2SD

NOTES: SD – standard deviation, OR- overall ratio, AR-anterior ratio (see explanation in the text).

2 groups, while comparing anterior ratio – in the individual malocclusion groups with Class 1, Class II, 1 and Class II, 2 abnormalities.

Originally Bolton suggested that the discrepancy greater than 1 standard deviation can cause clinical problems [Bolton W, 1958]. Most authors define a clinically significant ratio as 2 standard deviations compared to Bolton's norm [Crosby D, Alexander C, 1989; Freeman J et al., 1996; Santoro M et al., 2000; Araujo E, Souki M, 2003; Othman S, Harradine N, 2006]. By this definition an anterior ratio below 73.9% or above 80.5% and an

overall ratio below 87.5% or above 95.1 % would be considered clinically significant. According to Bolton U. and Proffit U., less than 5% of population has overall Bolton discrepancy, exceeding 2 standard deviations, but their studies included individuals with excellent occlusion [Bolton W, 1958; 1962; Proffit W et al., 2007].

In present study, the overall ratio discrepancies exceeding 2 standard deviations were found in 11.25% of studied population (10% greater than +2 standard deviations and 1.25% greater than -2 standard deviations). The prevalence of Bolton anterior ratio exceeding 2 standard deviations was detected in 28.75% of studied population (26.25% greater than +2 standard deviations and 2.5 % greater than -2 standard deviations). Discrepancy with Bolton norm exceeding 2 standard deviations was observed in 45% cases in patients with malocclusions of Class III. While comparing the anterior and overall ratios, it is noted, that in every malocclusion group, there is a greater percentage of patients with anterior mesio-distal tooth size discrepancies greater than 2 standard deviations from Bolton's mean compared with patients with overall discrepancies. This could be explained by the fact that tooth size abnormalities most frequently occur in the region of anterior teeth, especially maxillary

and mandibular incisors. The greater percentage of patients with anterior tooth size discrepancy in comparison with discrepancies in the overall ratio can be explained by the fact that the size of anterior teeth has, mathematically, less effect on overall ratio [Othman S et al., 2006]. The size and presence of the maxillary anterior teeth, particularly the lateral incisors, may differ within populations, for example, the most commonly congenitally absent teeth are the upper lateral incisors in European populations and the lower incisors in Chinese populations [Muller T et al., 1970; Davis P, 1987]. Bolton's ratios definitely increased in patients with peg-shaped lateral incisors. The results of the present study showed that a large number of orthodontic patients in Armenia have Bolton tooth size discrepancy exceeding 2 standard deviations, that may effect on treatment goals and results. Bolton tooth size analysis should be used for every orthodontic patient before initiation of treatment.

It can be concluded, that Bolton's ratios in orthodontic patients in Armenia differ from his standards. High percentage of the orthodontic patients has Bolton tooth size discrepancy exceeding 2 standard deviations. It is necessary to calculate Bolton's ratios in all orthodontic patients, especially in patients with malocclusions of Class III.

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CLINICAL RESEARCH

**ROSUVASTATIN AND FENOFIBRATE INFLUENCE ON ECHOCARDIOGRAPHIC AND BIOCHEMICAL PARAMETERS OF ENDOTHELIAL REACTIVITY DEPENDING ON POLYMORPHISM OF PPARG II PPARA GENES IN OBESE PATIENTS WITH ESSENTIAL HYPERTENSION**

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**ABSTRACT**

*The aim of study was determination of rosuvastatin and fenofibrate influence on echocardiographic and biochemical parameters of endothelial reactivity depending on polymorphism of PPARG u PPARA genes in hypertonic patients with obesity.*

*Totally 352 patients were examined, 332 of them with hypertonic disease of I-II stage, 1-2 grade and obesity, forming the experimental group and control group, consisting of 20 practically healthy individuals. The level of total cholesterol, triglycerides, high, low and very low density lipoproteins, uric acid, C-reactive protein and immunoreactive insulin were determined in serum levels of examined patients. Polymerase chain reaction was used to study polymorphism of PPARA and PPARG genes. Vasomotor endothelial function was investigated using ultrasound diagnostic complex Vivid-3 by the method of D. Celermajer with analysis of flow-mediated dilatation and index of peak flow. In turn, the experimental group was divided into 2 subgroups, 172 patients from those were treated with rosuvastatin in dose of 5-40 mg per day, and 160 patients – with fenofibrate of 200 mg per day.*

*A significant decrease of hyperlipidemia, insulin resistance and systemic inflammation parameters as well as their intercorrelation was found in both groups. Both preparations significantly increased post-ischemic hyperemia level (indices of flow-mediated dilatation and peak flow). Genotype Pro12Ala/Ala12Ala of PPARG gene was found more favorable for rosuvastatin treatment as well as genotype Leu162 Leu of PPARA gene for fenofibrate treatment. The best efficacy was found in patients with genotype Pro12Ala/Ala12Ala of PPARG gene during treatment with rosuvastatin and genotype Leu162Leu of PPARA gene in the group treated with fenofibrate.*

*Thus, it can be concluded, that rosuvastatin and fenofibrate on have positive impact on hyperlipidemia and insulin resistance in hypertonic patients with obesity. Dependency of treatment efficacy from gene polymorphism was also proved: for PPARG in terms of treatment Pro12Ala/Ala12Ala genotype was more favorable, as well as for PPARA – Leu162Leu.*

**KEYWORDS:** hypertonic disease, endothelium, rosuvastatin, fenofibrate, endothelium-dependent vascular reactivity, gene polymorphism.

**INTRODUCTION**

There is a growing body of evidence that endothelial dysfunction worsens the course of hypertension disease and causes the progression of ath-

erosclerosis in patients with the presence of cardiovascular risk factors, such as obesity. The main functional consequences are the reduction of the bioavailability of nitric oxide, increasing of expression of cytoadhesive molecules and components involved in the processes of thrombosis and fibrinolysis. Connection of endothelial dysfunction is well-proven with the increase of chole-

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terol, low density lipoproteins, which are accompanied by the increase of triglycerides, insulin resistance [Bocharova K, 2010; Babak O et al., 2011; Konopleva L, 2011; Belovol A et al., 2013]. Destructive vascular effect of hypertriglyceridemia is mainly due to the prevalence of atherogenic small dense particles of low density lipoproteins that was proven for the level of triglycerides above to 1.5 mmol/l [Malik J et al., 2001; Teragawa H et al., 2005; Uenoa H et al., 2011].

Chronic inflammation of vascular paries is also connected with endothelial dysfunction. The levels of C-reactive protein, interleukin-6 decreased while conducting lipid-lowering therapy [Malik J et al., 2001; Huang Y et al., 2003; Teragawa H et al., 2005; Uenoa H. et al., 2011].

The treatment of endothelial dysfunction in this group of patients also remains a not fully identified issue. There is evidence that statins improve endothelial function in patients with hypercholesterolemia [Chazova I et al., 2006; Drapkina O et al., 2012]. There are less data regarding the influence of fibrates on the improvement of endothelial function, there is information only about the population of patients with diabetes. Overall, the data on the effect of lipid-lowering therapy on endothelial function in combined hyperlipidemia is not enough. Pleiotropic metabolic effects of fenofibrate are mediated by PPAR $\alpha$  receptors, which can partially explain the influence of fenofibrate on vascular reactivity [Malik J et al., 2001; Huang Y et al., 2003; Teragawa H et al., 2005].

The implementation of technologies into clinical practice of so-called personalized medicine is one of the ways to improve the effectiveness and safety of pharmacotherapy. It is known that 50% of the adverse pharmacological responses (development of side effects or lack of efficacy) depend on the genetic characteristics of the patient. That is why clinical pharmacogenetics allows the individualization of choice of medical drugs and their dosage regimes based on the study of individual patient genotype.

Peroxisome proliferator-activated receptors (PPAR $\alpha$ ,  $\beta/\delta$ ,  $\gamma$ ) are nuclear hormone receptors, which do not only control the activity of many genes, but also are central regulators of lipid and carbohydrate metabolism, differentiation and development of adipose tissue, modulators of gene

expression in many tissues including adipocytes, epithelial cells, smooth muscle, macrophages and vascular endothelium. The effectiveness of various types of PPAR agonists (fibrates, glitazones and glitazars) depending on gene polymorphism receptors PPAR is currently investigated. The ability to activate PPAR ligands of low molecular weight can effectively affect these diseases [Lupinskaya Z et al., 2008; Sidorchuk L, 2009; Belfort R et al., 2010; Belovol A et al., 2013]. The achievements in the study of physiology and pathology of PPAR in recent years allow us to consider this directivity as one of the most promising in controlling of the development of atherosclerosis, essential hypertension and diabetes of 2<sup>nd</sup> type. Therefore, the conduction of molecular genetic researches for the study of gene polymorphism, involved in the regulation of carbohydrate and lipid metabolism is certainly actual and necessary.

The aim of study was rosuvastatin and fenofibrate influence on echocardiographic and biochemical parameters of endothelial reactivity depending on polymorphism of PPARG и PPARA genes in obese patients with essential hypertension.

#### MATERIAL AND METHODS

*Contingent of surveyed patients and their clinical characteristics:* The study is based on a survey of 352 patients, who were divided into groups. Experimental group was consisted of 332 patients with hypertonic disease of I-II stage, 1-2 grade and obesity, who were hospitalized in the clinic of SI "National Institute of Therapy named after L.T. Malaya NAMS of Ukraine". The control group consisted of 20 practically healthy persons who were not taking any drugs and without cardiovascular risk factors, matched by age and sex.

Among examined were 185 (55.72%) men, 147 (44.38%) women, average age was 53.0 $\pm$ 6.5 years. Body weight of the examined patients was 91.7 $\pm$ 12.0 kg, body mass index – 32.3 $\pm$ 3.9 kg/m<sup>2</sup>. Initial numbers of office systolic blood pressure and diastolic blood pressures were about 161.7 $\pm$ 3.0 and 96.9 $\pm$ 2.5 mm Hg respectively; heart rate was 74.6 $\pm$ 0.7 beats/min.

Obesity in patients was defined according to the criteria defined in the European guidelines for the treatment of hypertension in 2013 [ESH/ESC, 2013]. Data were analyzed with the standard anthropometric variables waist circumference, hip circumference, fasting glucose, the value of immunoreactive insulin, triglycer-

ide levels and high-density lipoprotein cholesterol, total cholesterol and low density lipoprotein levels in accordance with the recommendations of the International Diabetes Foundation [IDF, 2005].

The study excluded patients with type 1 diabetes, verified symptomatic arterial hypertension, clinical signs of coronary heart disease, by the level of office blood pressure  $> 180/110$  mm Hg, uncompensated liver's diseases (transaminase levels above normal in 3 times), acute or chronic renal insufficiency (serum creatinine  $>133$  mmol/l for men and 124 mmol/l for women), myocardial infarction or acute stroke in history, pregnancy and lactation.

Hypertensive patients were divided into first and second experimental groups depending on the intended treatment. First experimental group consisted of 172 patients treated with rosuvastatin at a dose of 5-40 mg per day, link of treatment effectiveness with polymorphism of PPARG gene was studied in 130 of these patients. The second group was consisted of 160 patients who were treated with fenofibrate of 200 mg, the dependency of treatment efficacy from polymorphism of PPARA gene was studied in 126 of these patients. All patients received antihypertensive therapy in form of telmisartan 20-80 mg per day at early stages of treatment. Assessment of the dynamics parameters were within 6 months after therapy.

*Laboratory methods:* The level of total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, very low density lipoproteins and uric acid was determined in serum, which was taken from the cubital vein, after a 12-hour fast by enzymatic method photolorimetry recruitment firm "Human" (Germany).

The determination of C-RP and immunoreactive insulin was performed by an ELISA using appropriate kits firm "DRG-Diagnostics" (USA) with ELISA photolorimeter "HUMAREADER" firm "Human" (Germany). According to the regulations of techniques used in the study, fasting immunoreactive insulin concentration is considered normal if it does not exceed 25 mcE/ml.

The study of PPARG and PPARA gene polymorphism performed on the basis of the polymerase chain reaction and restriction analysis by horizontal agarose gel electrophoresis.

*Instrumental methods:* The vascular motor function of endothelium was measured by deter-

mining the dynamics of blood flow in the brachial artery during reactive hyperemia. The evaluation was conducted on the ultrasonic diagnostic complex Vivid-3 (General Electric, USA), 7.5 MHz linear transducer (resolution 0.01mm) by the procedure described by D. Celermajer and co-authors [Celermajer D et al., 1992]. All vasoactive drugs were canceled to patient a day before the test, diuretics – per 2 days, amlodipine - up to 5 days. On the day of study, patients refused to drink coffee, strong tea, alcohol, cigarettes. In the morning patients underwent scanning of the brachial artery on an empty stomach with air temperature  $+ 22^{\circ}$  C. The patient was in the supine position for 10-15 minutes, and then use of vascular sensor determined the base diameter of the brachial artery in the zone between the endothelium and media at a maximally clear image of front and rear walls of the vessel. The settings were kept constant throughout the study. Reactive hyperemia was achieved by pumping of pneumatic cuff up to 200 mm Hg, superimposing on shoulder for 5 minutes. All measurements were carried out in diastole. Measurement of brachial artery diameter was performed on 80 second after compression. The expansion of brachial artery testifies to the preservation of endothelial function by 10% and more, while endothelial dysfunction - less than 10%.

One of ultrasonic methods for the study of endothelial function in modern medicine is the study of endothelium-dependent vasodilation or flow-dependent dilation. But back in 2001 [Malik J et al., 2001], there were data that confirmed the high sensitivity and representativeness of such parameter, the maximum blood flow velocity (ml/min) or the index of the peak flow. It was proved that index of peak flow closely correlates with changes in blood flow induced by intra-arterial infusion of acetylcholine (a method which is widely used in the assessment of endothelial function). Unlike flow-mediated dilation, blood flow parameters reflect "average" vascular reactivity relative to large proportion of arterial network [Malik J et al., 2001; Furuhashi M et al., 2002].

Blood flow was measured at rest and after removal of the cuff as the average of three cardiac cycles (except the first usually deformed cycle). Index of peak flow was calculated as the integral of blood flow velocity multiplied by the cross-



tion of the vessel in early postischemic period.

Statistical processing of the results was performed on a personal computer using the software package "SPSS 16.0 for Windows" on the basis of electronic database created by us. Before statistical processing, the assessment of obtained data conformity was carried out by normally distributed random variables. In most cases, the results were not consistent with the law of normal distribution, that's why nonparametric tests were used. Average values and their standard error were calculated for groups ( $M \pm m$ , where  $M$  – mean value,  $m$  – its standard error). For comparison, the average values were used nonparametric Mann-Whitney test for independent samples. Correlations were evaluated by Spearman's correlation coefficient ( $\rho$ ). The probability of changes in the parameters before and after treatment was evaluated by the nonparametric Wilcoxon test for dependent samples. The results, for which the level of significance ( $p$ ) didn't exceed 0.05, were considered as reliable.

## RESULTS AND DISCUSSION

### Ultrasonic characteristics of endothelial function

Normal significance of ultrasound indices were based on a survey of the control group. In the group of healthy volunteers vascular reactivity indices were as follows: Endothelium-dependent vasodilation –  $4.75 \pm 2.52\%$ , index of peak flow –  $896.3 \pm 35.6$  ml/min.

The results of studies are shown in Table 1. The differences between the effects of drugs on ultrasound parameters were not found. A significant increase of endothelium-dependent vasodilation was

found while taking these drugs. Also there was a significant change in reactive hyperemia index after treatment: index of peak flow was significantly increased after treatment with both drugs.

**Biochemical parameters:** The results of biochemical analysis are shown in Table 2. Rosuvastatin exceeded fenofibrate in decrease of serum levels of total cholesterol, low density lipoprotein

TABLE 1.

Changes of ultrasonic parameters in vascular reactivity after treatment with fenofibrate and rosuvastatin

Indicators	Before	After	p
Group treated by fenofibrate			
Endothelium-dependent vasodilation (%)	2.26±0.9	2.98±0.8	<0.05
Index of peak flow (ml/min)	448.0±8.9	546.1±11.0	<0.01
Group treated by rosuvastatin			
Endothelium-dependent vasodilation (%)	2.19±0.6	2.87±0.9	<0.05
Index of peak flow (ml/min)	453.2±9.3	570.0±11.7	<0.01

and non-high density lipoprotein cholesterol. Fenofibrate was more effective in reduction of serum triglycerides and increase of high density lipoprotein cholesterol. Both drugs reduced C-reactive proteins and insulinemia. However, this reduction was significantly reliable only for fenofibrate.

The detection of insulin effect on C-reactive proteins confirms the literature data about the cor-

TABLE 2.

Changes in biochemical parameters after treatment with fenofibrate and rosuvastatin

Indicators	Fenofibrate group		Rosuvastatin group	
	Initial values	After treatment	Initial values	After treatment
C-reactive protein (mg/l)	11.9±0.1	5.8±0.09**	10.8±0.13	8.9±0.12
Insulinaemia (mcE/ml)	18.2±1.2	12.9±0.72*	17.7±2.0	16.5±0.82
Uric acid (mmol/l)	418±2.05	308±6.0*	411±2.21	387±8.2
Triglycerides (mmol/l)	2.01±0.04	1.52±0.10**	2.10±0.05	1.57±0.04**
Cholesterol (mmol/l)				
Total	5.75±0.16	4.64±0.09**	5.96±0.12	3.44±0.05***
Low density lipoprotein	3.76±0.10	3.05±0.06	3.39±0.09	1.90±0.05***
High density lipoprotein	1.06±0.02	1.22±0.06**	1.19±0.07	1.25±0.02
Non-high density lipoprotein	4.7±0.03	3.2±0.01***	4.8±0.04	2.3±0.09***

NOTES: \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

reduction of systemic inflammation fenofibrate. Thus, fenofibrate significantly reduced high-strung C-reactive proteins in insulin-resistant patients with metabolic syndrome without diabetes on  $49.5 \pm 8\%$  ( $p=0.005$ ), as well as interleukin-6  $29.8 \pm 7\%$  ( $p=0.03$ ) in comparison with placebo [Binggeli C et al., 2003]. According to other authors, fenofibrate both in experimental and clinical studies also had the ability to adjust insulin resistance [Florez J et al., 2007, Li P et al., 2010]. However, the information on the reduction of insulinemia is contradictory.

*Correlation of biochemical parameters and indices of vascular reactivity:* Possible correlations were not found before the treatment. The analysis of treatment effects revealed a significant correlation between the decrease of insulinemia and improvement of both indicators of vascular reactivity in the treatment with fenofibrate (Table 3). Index of peak flow was significantly improved inversely proportional to changes of total cholesterol during the treatment with rosuvastatin, and endothelium-dependent vasodilation also had a similar dependence on the totals of non-high density lipoprotein cholesterol.

*Study of the treatment efficacy depending on the polymorphism of genes:* The efficacy of therapy depending on the genotype polymorphism of PPARG gene was studied in 130 patients of the rosuvastatin group.

Positive changes were observed among all indicators of endothelium structural and functional state on the background of the prescribed therapy.

Positive effect of the treatment was more clearly established in Pro12Ala carriers of Pro12Ala/Ala12Ala genotype of polymorphism than in carriers of genotype Pro12Pro during the dynamic study of endothelium structural and functional state, which testified to the genetically determined, more directed pathogenic effect of the proposed therapies. However, while comparing, some difference were observed in carriers of genotypes Pro12Pro and Pro12Ala/Ala12Ala of Pro12Ala polymorphism of PPARG gene (Table 4).

As it can be seen from Table 4, in both subgroups changes in the indices after treatment were significant, but the values of the parameters of endothelial ultrasound in patients with genotypes Pro12Ala/Ala12Ala after the treatment were significantly higher than those in patients with genotype Pro12Pro, whereas baseline were not significantly different. That is, in case of genotypes Pro12Ala/Ala12Ala, the response to therapy with rosuvastatin was better conditioned and significantly more expressive positive dynamics in structural and functional state of the endothelium in patients with hypertensive disease, while in genotype Pro12Pro of PPARG gene the character of response to therapy with rosuvastatin was worse.

Also, the efficacy of therapy depending on the polymorphism of PPARA gene was studied in 126 patients of the fenofibrate group. Leu162Leu genotype was diagnosed in 35 of them, in 91 – Leu162Val. Therapy with fenofibrate induced positive changes of all indicators of endothelium structural

**TABLE 3.**  
Correlation between biochemical and vascular effects during the treatment with fenofibrate and rosuvastatin (according to Spearman)

Indicators	Index of peak flow		Endothelium-dependent vasodilation	
	Fenofibrate	Rosuvastatin	Fenofibrate	Rosuvastatin
C-reactive protein (mg/l)	0.22	-0.29	0.18	0.23
Insulinaemia (mcE/ml)	-0.56*	-0.37	-0.40*	0.18
Uric acid (mmol/l)	0.24	0.15	0.04	0.05
Triglycerides (mmol/l)	-0.24	-0.26	-0.30	0.29
<b>Cholesterol (mmol/l)</b>				
Total	0.27	-0.42*	0.32	-0.43*
Low density lipoprotein	0.32	-0.02	0.41	0.45*
High density lipoprotein	0.06	0.08	-0.29	0.17
Non-high density lipoprotein	0.05	-0.5	0.22	0.38*

NOTES: \* Significant correlation ( $p < 0.05$ );  $p > 0.05$  in other cases.

TABLE 4.

Changes of ultrasonic parameters of vascular reactivity							
Indicators	Before Treatment	After Treatment	P	Before Treatment	After Treatment	P	P <sub>1</sub>
<b>Treatment with rosuvastatin depending on polymorphism of PPARG gene</b>							
	Pro12Pro (n=28)			Pro12Ala/Ala12Ala (n=102)			
IPF, ml/min	448.5±19.8	492.3±18.2	<0,05	458.6±10.2	587.5±14.3	<0.01	<0.001
EDVD, %	2.23±1.0	2.76±0.9	<0,05	2.17±0.6	3.15±0.7	<0.001	<0.01
<b>Treatment with fenofibrate depending on polymorphism of PPARA gene</b>							
	Leu162Leu (n=35)			Leu162Val (n=91)			
IPF, ml/min	453.3±12.1	562.1±14.6	<0.01	478.0±10.4	529.3±12.3	<0.05	<0.01
EDVD %	2.15±1.0	3.07±0.8	<0.01	2.28±0.7	2.86±0.9	<0.05	<0.01

**Note:** IPF- index of peak flow, EDVD-endothelium-dependent vasodilatation, p<sub>1</sub>-difference between genotypes after treatment.

and functional state, however, while comparing, some differences were observed in such carriers of genotypes Leu162Leu and Leu162Val of PPARA gene: indicators of endothelium structural and functional state in genotype Leu162Leu were better than in genotype Leu162Val. In other words, likewise polymorphism of PPARG gene, the changes of indicators in both subgroups were significant after treatment, but the response on therapy with fenofibrate was the best in patients with genotype Leu162Leu, although this genotype was much rarer.

Therefore, rosuvastatin reduced total cholesterol and non-high density lipoprotein cholesterol, significantly higher compared with fenofibrate. Fenofibrate better reduced the level of triglycerides, C-reactive proteins and increased high density lipoprotein cholesterol. Fenofibrate also reduced the appearance of insulinemia, although no significant difference between rosuvastatin and fenofibrate on the effect of this measure was found.

Despite various metabolic effects of drugs, their effects on vascular reactivity were similar. Both drugs significantly improved endothelial state

(growth of endothelium-dependent vasodilation and index of peak flow).

Reduction of manifestations of chronic inflammation and insulin resistance (the dynamics of C-reactive proteins and insulin levels) under the influence of fenofibrate significantly resulted in improved endothelial function, meanwhile, endothelium protective effect of rosuvastatin was more depended on changes in lipid levels (as evidenced by the probable correlation between vascular reactivity and levels of total and non-high density lipoprotein cholesterol (p<0.05)).

The best efficacy was observed in patients with genotype Pro12Ala/Ala12Ala of polymorphism of PPARG gene on the background of treatment with rosuvastatin and genotype Leu162Leu polymorphism of PPARA in the group treated with fenofibrate.

The prospect of further research can be a comparison of parameters of endothelial dysfunction and the effectiveness of hypolipidemic therapy in patients with arterial hypertension and obesity and normal body weight.

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