Arterial stiffness in hypopituitary patients with life--long growth hormone deficiency

Jerzy Kosowicz[1], Ziad El Ali[1], Andrzej Wykrętowicz[2], Tomasz Krauze[2], Przemysław Guzik[2]

[1] Department of Clinical Endocrynology, University School of Medicine, Poznań, Poland

[2] Department of Internal Medicine, Division of Cardiology-Intensive Therapy, University School of Medicine, Poznań, Poland

Abstract: Introduction. Patients with hypopituitarism have a shorter survival period and premature mortality due to cardiovascular complications. **Objectives.** The aim of our study was to evaluate the arterial stiffness and hemodynamic parameters based on pulse wave analysis in 22 adult patients with long-life growth hormone (GH) and insulin-like growth factor 1 (IGF-1) deficiencies, lasting from 22 to 57 years. **Patients and methods.** In all patients, a combined pituitary hormone deficiency was diagnosed. All patients were on substitution therapy, receiving levothyroxine, sex hormones and hydrocortisone (when required), but none of the patients had ever received recombinant GH therapy. A control group consisted of 36 healthy subjects strictly matched to patients by age and body mass index. In the patients and control subjects pulse wave analysis was performed with the use of Sphigmocor MX reconstructing the aortic pulse wave in a real time. **Results.** The peripheral and central augmentation indexes were significantly increased in the hypopituitary patients compared with the control subjects. The central pulse pressure was also elevated in the patients. These hemodynamic parameters pointed to an increased arterial stiffness. **Conclusions.** In patients with hypopituitarism, the life-long GH and IGF-1 deficiencies lead to an increase in the arterial stiffness.

Key words: arterial stiffness, growth hormone deficiency, hypopituitarism

INTRODUCTION

Arterial stiffness is associated with a negative prognosis due to cardiovascular complications [1-4]. Arterial stiffness can be measured indirectly using the augmentation index or augmentation pressure. Changes in smooth muscle tone lead to a reduction in artery elasticity. It is associated with the increase difference between systolic and diastolic blood pressure. Arterial stiffness can be measured indirectly by analysis of pulse-wave. The augmentation index and easy measure pulse pressure are markers of aortic stiffness and can indicate an increased cardiovascular risk [5-7].

Hypopituitary in adults is associated with a cluster of cardiovascular risk factors, including higher blood pressure, insulin resistance, dyslipidaemia, elevated level of cholesterol, mainly low-density lipoproteins (LDL) cholesterol, decreased level of high-density lipoproteins cholesterol and elevated level of triglycerides [8,9]. Hypopituitary patients very often demonstrate overweight and obesity with the body mass index (BMI) exceeding 25 kg/m^2 [9].

Some retrospective studies have shown that hypopituitarism in adult patients lasting from 4 to 15 years may be associated with the twofold increased causes of death resulting from cardiovascular complications [10]. Tomlinson et al. [11] demonstrated that growth hormone (GH) deficient patients have shorter overall survival due to cardiovascular complications includindg heart infarction, aneurysm or cerebral ischemia.

The aim of this study was to evaluate the arterial stiffness and hemodynamic parameters based on pulse wave analysis in patients with life-long growth hormone deficiency.

PATIENTS AND METHODS

Twenty-two hypopituitary patients with GH-deficiency diagnosed in childhood were enrolled in to the study. The studied group consisted of 13 males and females, aged 25–66 years. The diagnosis of hypopituitarism was made at the ages of 3–6 years, based on hormonal tests, physical examination and radiological imaging. Radioimmunological methods of GH assessment revealed low GH level at resting and no increase in provocative tests. The patients were treated with levothyroxine at a dose of 50–100 µg a day, anabolic steroids (metandienon, oksandrolon) and in the case of secondary adrenocortical insufficiency hydrocortisone at a of dose 20 mg a day. Hypopituitarism in all patients was diagnosed 2–4 decades earlier, before introducing recombined growth hormone (rGH) to the treatment. Thereby the patients were not receiving replacement therapy for GH. The patients had signs of delayed puberty, and therefore after the age of 14 years testosterone replacement therapy was began in men (0.1 g every two

Correspondence to:
prof. dr hab. med. Jerzy Kosowicz, Klinika Endokrynologii i Przemiany Materii, Uniwersytet Medyczny im. Karola Marcinkowskiego, ul. Przybyszewskiego 49, 60-355 Poznań, Poland, phone: +48-61-869-13-56, fax: +48-61-869-16-82, e-mail: jkosowicz@poczta.fm
Received: June 8, 2007. **Accepted in final form:** August 3, 2007.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2007; 117: (5-6): 221-226

Table 1. Clinical and biochemical characteristics 22 hypopituitary patients

	Mean ±standard deviation	Range
Age (years)	51 ±14.1	26–69
Time of disease (years)	40.6 ±15.7	22–57
Gender (W/M)		9/13
Weight (kg)	57.9 ±13.2	35–86
Height (cm)	144.4 ±12.4	127–162
BMI (kg/m^2)	27.2 ±5.1	20–38
Fat mass (%)	32.7 ±8.1	13.4–51.3
Total cholesterol (mg/dl)	254.3 ±46.8	176–378

Data are given as mean ±SD
BMI – body mass index

weeks) and estrogene replacement therapy in women. Despite systematic testosterone replacement therapy, the men still had signs of delayed puberty, testes were small and soft. During the study the patients height ranged from 127 to 162 cm with the mean 144 ±12.4 cm, their body weight was from 35 to 86 kg with the mean 57.9 ±13.2 kg, and body mass indexes were 20–38 kg/m^2. Total fat masses in our study group, except for one case, were increased and reached more than 25%, even in patients with a normal BMI. Clinical and biochemical parameters of the patients with hypopituitarism are detailed in Table 1.

Hand X-rays of the wrist revealed ended bone ages in 21 patients. The cranium X-ray showed a hypoplastic facial skeleton compared with a normal craniocerebral. The sella turcica was of a normal size in 15 cases, significantly decreased in 5 cases and enlarged in 2 cases. The magnetic resonance imaging of the hypothalamic-pituitary region revealed pathologic changes in all patients except for one case. The size of anterior pituitary was decreased in 21 patients; its height was 2–3 mm instead of 5–8 mm like in the healthy control group. Other sizes of adenohypophysis were slightly decreased. The pituitary stalk was thinner, elongated in 7 cases and broken in 5 cases; in these patients the posterior pituitary was located ectopically.

Hormonal tests revealed panhypopituitarism in all patients. The levels of GH were low, also on an insulin stress test after adequate hypoglycemia. The maximum GH on an insulin stress test was 0–2.1 ng/ml. Diagnostic, provocative tests were several times repeated with the same results. Low levels of the insulin-like growth factor 1 (IGF-1) ranging from 11 to 58 ng/ml significantly differed from a normal range (100–300 ng/ml). The decreased level of the protein binding IGFBP3 was 0.6–1.2 µg/ml (normal: 1.0–7.0 µg/ml). Other hormonal tests are detailed in Table 2. In laboratory tests, elevated levels of total cholesterol and the LDL fraction were observed in most of the patients. Seven patients had hypertension.

The study selection criteria excluded patients who received rGH replacement therapy with partial somatothropin hypopituitarism, if increased GH on an insulin stress test exceeded 3 ng/ml or IGF-1 level was more than 100 ng/ml, and patients with cardiovascular diseases (heart infarct, cerebral ischemia) in history. Several patients were not admitted to the study due to death, threefold heart infarct and recurrent cerebral strokes, which confirmed other authors' thesis about an increased frequency of cardiovascular events.

The control group consisted of 36 healthy persons matched for age and the BMI. The mean ages in hypopituitary patients and the control group were 48 ±15.1 and 46 ±13.3 years, respectively. The body mass indexes were 26.8 ±4.9 kg/m^2 in hypopituitary patients, and 26.1 ±4.0 kg/m^2 in the control group. The patients' height was 145 ±14.3 cm in comparison with the control group where it reached 171 ±9.3 cm. All patients gave their informed consent to participate in the study.

Hemodynamic measurements

Peripheral pulse pressure waveforms were recorded non-invasively from the radial artery using Sphygmocor MX (Atcor Medical, program 7.0). Subjects were examined on an empty stomach, after resting, without cigarette smoking. The central pressure waveform was derived by mathematical transformation of the peripheral pressure waveforms using a generalized validated transfer function. Data received this way approximate to similar readings gathered from invasive recordings. Based on the pulse wave analysis, rate of the heart and the time of left ventricular ejection were assessed. At the level of aorta – systolic and diastolic blood pressure and the markers of arterial stiffness, that is central augmentation pressure (cAI) and peripheral augmentation pressure (pAI), as well as augmentation pressure were obtained. The augmentation index is the ratio of the second peaks of pulse pressure to the first systolic

Table 2. Hormonal tests in 22 patients with childhood onset hypopituitarism

Hormone deficiency	Number of patients	Results of diagnostic tests
GH and IGF-1 deficiency	22	GH in insulin test <2.2 ng/ml IGF-1: 11–58 ng/ml
TSH deficiency	14	FT_4 <9 pmol/L
LH and FSH deficiency	22	LH <1.1 IU/L FSH <1.2 IU/L
Prolactin deficiency	4	prolactin <2 ng/ml
ACTH deficiency		
DHEA-S	16	DHEA-S <100 ng/ml
Cortisone	5	cortisone level in the morning <5 µg/dl

ACTH – adrenocorticotropic hormone, DHEA-S – dehydroepiandrosteronum sulphatum, FSH – follicle stimulating hormone, FT_4 – free tyroxine, GH – growth hormone, IGF-1 – insulin-like growth factor 1, LH – luteinizing hormone, TSH – thyroid stimulating hormone

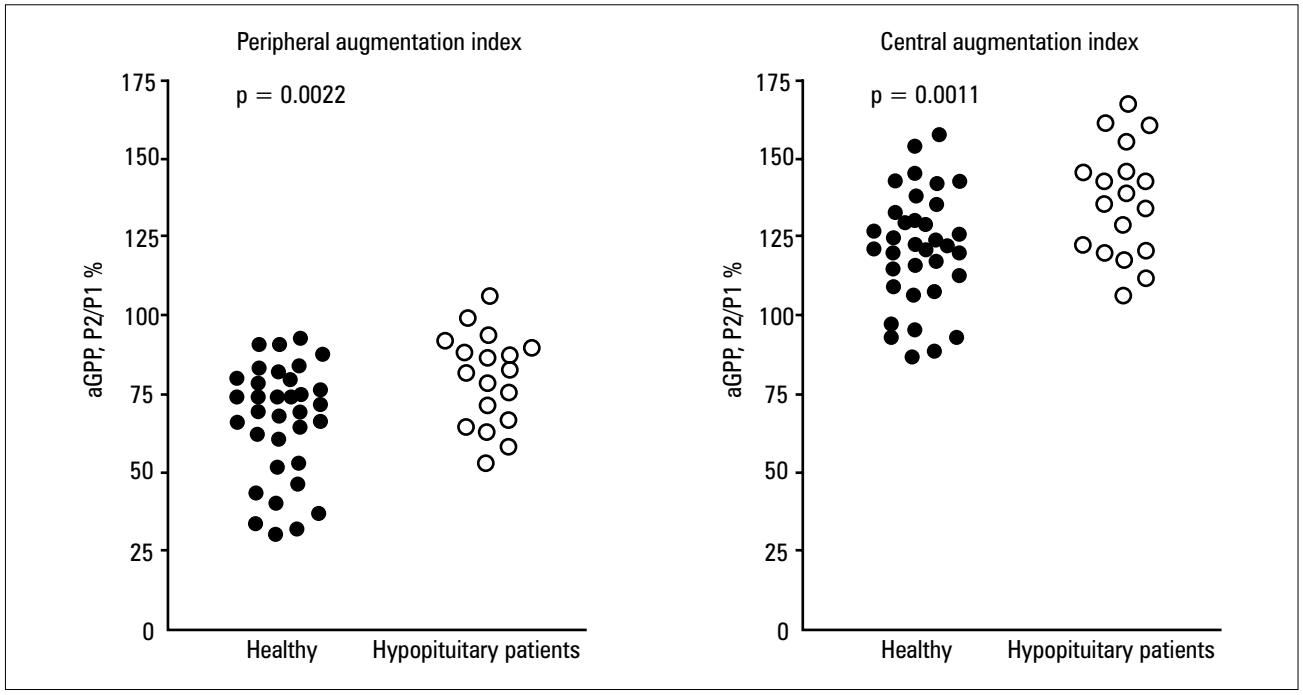

Fig. 1. Peripheral and central augmentation index in hypopituitary patients and in the healthy control group

peaks. Moreover, the amplification index was determined as the ratio of peripheral pulse pressure to central pulse pressure.

Hormonal determination

The levels of adrenocorticotropic hormone, GH, somatomedin C, IGF-1, follicle stimulating hormone and luteinizing hormone were measured using the radioimmunologic method, but prolactin, free tyroxine, triiodothyronine and thyroid stimulating hormone were determined using the electrochemiluminometric assay (COBAS, Mannheim, Germany). The body mass density was evaluated by the densitometry method using Lunar DPX (Lunar Corporation, Madison, USA) with program 3.63

Statistical analysis

All statistical analyses were performed using the nonparametric Mann and Whitney test (SPSS version 7.5 for Windows, SPSS, Inc., Chicago, IL). Results are expressed as the mean ± standard deviation; a p value of less than 0.05 was considered significant.

RESULTS

The heart rate was similar between hypopituitary patients and the control group (69 ±9.4 and 72.1 ±13.1 per minute, respectively). The values of systolic and diastolic blood pressure were 118.4 ±24.3 mmHg and 72.1 ±14.1 mmHg in hypopituitary patients and were similar to the values in the control group (117.7 ±14.7 mmHg, 70.8 ±14.7 mmHg ±11.6 mmHg).

In addition, pAI in hypopituitary patients was 78.9 ±14.6% and was statistically significantly higher (p <0.002) than in the control group (66.5 ±17.7%). In hypopituitary pa-

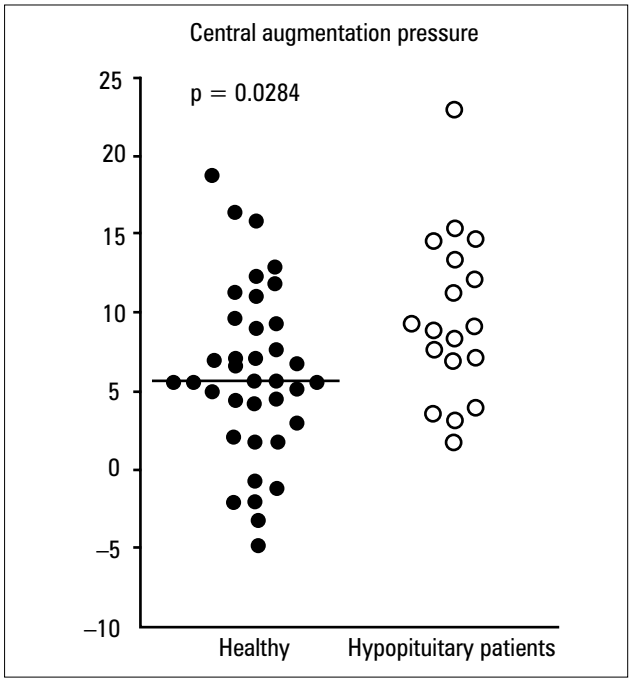

Fig. 2. Central augmentation pressure in hypopituitary patients in comparison to healthy subjects

Table 3. Results of hemodynamic findings in hypopituitary patients and in the control group

Parameter	Hypopituitarism		Control		P
	mean ±standard deviation	range min–max	mean ±standard deviation	range min–max	
Heart rate/min	69.0 ±9.4	53.9–86.0	72.1 ±13.1	53.3–113.8	NS
Time of cardiac output (ms)	314.6 ±21.3	256.8–341.8	322.2 ±20.2	283.6–356.9	NS
Peripheral systolic pressure (mmHg)	118.4 ±24.3	90.7–187.0	117.7 ±14.7	82.8–155.0	NS
Peripheral diastolic pressure (mmHg)	71.9 ±14.1	57.2–43.0	70.8 ±11.6	50.2–99.5	NS
Peripheral augmentation index (%)	78.9 ±14.6	52.0–104.5	66.5 ±17.7	30.0–92.5	<0.002
Central systolic pressure (mmHg)	108.5 ±23.0	85.4–170.6	105.2 ±14.4	76.9–139	NS
Central diastolic pressure (mmHg)	73.0 ±14.4	57.8–114.9	71.8 ±11.8	52.1–102.0	NS
Central augmentation index (%)	136.4 ±17.9	105.9–167.7	120.9 ±17.7	86.4–156.9	<0.001
Central augmentation pressure (mmHg)	9.4 ±5.3	1.4–22.8	5.6 ±5.1	5.0–16.5	NS
PPP (mmHg)	46.4 ±12.6	29.4–74.0	46.9 ±7.7	30.1–66.4	NS
CPP (mmHg)	35.5 ±10.6	22.0–56.6	33.3 ±6.8	22.4–49.7	<0.028
PPP/CPP	1.3 ±0.1	1.1–1.7	1.4 ±0.1	1.1–1.8	<0.037

NS – not signifficant, CPP – central pulse pressure, PPP – peripheral pulse pressure

tients cAI was elevated, the mean was 136.4 ±17.9%, while in the control group it was 120.9 ±17.7%.The differences were significant (p <0.001), as shown in Figure 1.

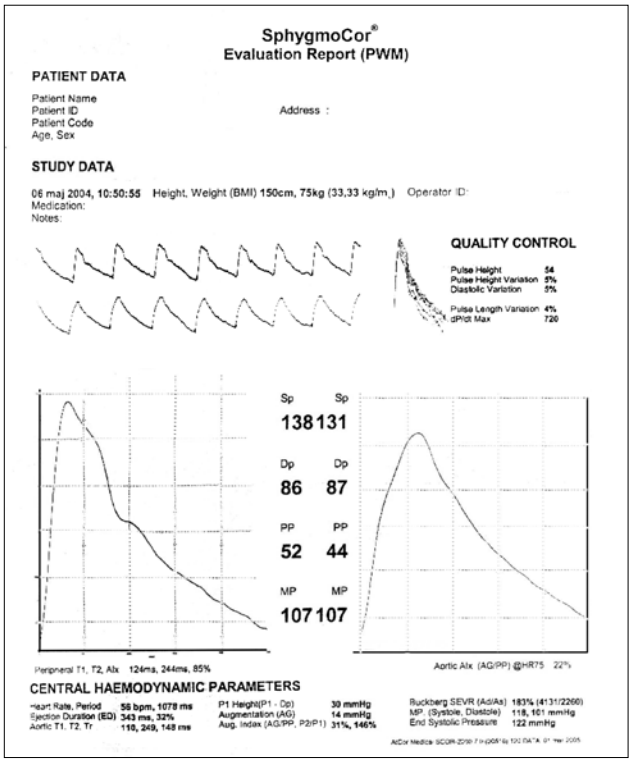

Fig. 3. Example of hemodynamic findings in hypopituitary patients

Central augmentation indexes in hypopituitary patients were 9.4 ±5.3 mmHg and were significantly higher than in the control group (5.6 ±5.1 mmHg; Fig. 2). A typical example of hemodynamic changes in hypopituitary patients is presented in Figure 3. Other parameters are shown in Table 3.

The results of hemodynamic findings in the studied group were compared with the BMI and the percentage of a total fat mass, because elevated levels of these markers are independent risk factors of cardiovascular complications. The correlations between the BMI and the augmentation index as well as between the percentage of fat mass and the augmentation index were not statistically significant.

DISCUSSION

Until now hemodynamic tests have been performed only in adult GH deficient patients with hypopituitarism [12-20]. Smith et al. [12] investigated arterial stiffness in 32 patients with GH-deficiency and reported that observed in GH deficient patients cAI values (23 ±12%) which were elevated in comparison with the healthy control group (14 ±14%) improved after 6 months of GH replacement therapy. The findings came from the radial artery made among seven GH deficient patients. In these patients, the values of pAI were significantly higher than in the control group [13].

In contrast to studies of adulthood onset GH deficiency, our studies were carried out among patients with childhood onset GH deficiency, lasting from 22 to 57 years. The obtained data showed increased arterial stiffness in the patients, confirmed by the increased mean augmentation index and

elevated central augmentation pressure. In our group of the patients the use of cigarettes and caffeine was significantly lower than in the control group, and thus it might have been expected that arterial stiffness in the studied group could be lower because of a well known negative influence of cigarettes and caffeine on the circulation system. The increased BMI and elevated level of total cholesterol despite of the use of the optimal dose of levothyroxine, as well as hypertension observed in 7 patients presented a significant load for their circulatory systems [21-23].

The major peripheral role of GH is performed through IGF-1 [24]; both hormones levels were significantly decreased in patients with childhood onset hypopituitarism. Coalo et al. investigated the correlation between the axis of GH/IGF-1 and atherosclerotic changes based on the intima/media index among 174 healthy persons aged 18–80 years. The authors reported a significant, reversible correlation between the IGF-1 level and early atherosclerotic changes, which indicated the role of low IGF-1 level and its IGFBP-3 in pathogenesis of atherosclerosis [25]. The overexpression of IGF-1 in human coronary artery endothelial cells were found, and this confirmed the direct influence of IGF-1 on these vessels [26]. Thus it may be supposed that long-life IGF-1 deficiency contributes to the reduction in artery elasticity.

Our data indicate that life-long GH and IGF-1 deficiency in patients with hypopituitarism is an independent risk factor for arterial stiffness, which may contribute to increased cardiovascular complications in these patients.

REFERENCES

1. Boutouyrie P, Tropeano AI, Asmar R, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension. 2002; 39: 10-15.
2. Gatzka CD, Cameron JD, Kingwell BA, Dart AM. Relation between coronary artery disease, aortic stiffness and left ventricular structure in a population sample. Hypertension. 1998; 32: 575-578.
3. Blacher J, Guerin AP, Pannier B, et al. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999; 99: 2434-2439.
4. Wykrętowicz A, Guzik P, Kąsinowski R, et al. Augmentation index, pulse pressure amplification and superoxide anion production in patients with coronary artery disease. Int J Cardiol. 2005; 99: 289-294.
5. Numberger J, Keflioglu-Scheiber A, Opazo Saez A, et al. Augmentation index is associated with cardiovascular risk. J Hypertens. 2002; 20: 2407-14.
6. Kennel WB. Hypertension in the elderly: epidemiologic appraisal from the Framingham Study Cardiol Eldery. 1993; 1: 359.
7. Posadzy-Małaczyńska A, Wanic-Kossowska M, Tykarski A, et al. Sztywność dużych naczyń u chorych z przewlekłą niewydolnością nerek leczonych zabiegami hemodializ (HD). Pol Arch Med Wewn. 2005; 114: 1072-1078.
8. Franklin SS, Khan SA, Wong ND, et al. Is pulse pressure useful in predicting risk for coronary artery disease? The Framingham Heart Study. Circulation. 1999; 100: 354-360.
9. Bohdanowicz-Pawlak A, Szymczak J, Bladowska J, et al. Risk factors of cardiovascular disease in GH-deficient adults with hypopituitarism: a preliminary report. Med Sci Monit. 2006; 12: CR75-80.
10. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet. 1990; 336: 285-288.
11. Tomlinson J, Holden N, Hills RK, et al. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet. 2001; 357: 425-431.
12. Smith JC, Evans LM, Wilkinson I, Goodfellow J, et al. Effects of GH replacement on endothelial function and large-artery stiffness in GH- deficient adults: a randomized, double-blind, placebo-controlled study. Clin Endocrinolo. 2002; 56: 493-501.
13. Irving RJ, Carson MN, Webb DJ, Walker BR. Peripheral vascular structure and function in men with contrasting GH levels. J Clin Endocrinol Metab. 2002; 87: 3309-3314.
14. Fazio S, Cittadini A, Sabatini D, et al. Growth hormone and heart performance. A novel mechanism of cardiac wall stress regulation in humans. Eur Heart J. 1997: 18; 340-347.
15. Minczykowski A, Gryczynska M, Ziemnicka K, et al. The influence of growth hormone (GH) therapy on cardiac performance in patients with childhood onset GH deficiency. Growth Horm IGF Res. 2005; 15: 156-164.
16. Sartorio A, Ferrero S, Conti A, et al. Adults with childhood onset growth hormone deficiency: effects of growth hormone treatment on cardiac structure. J Intern Med. 1997; 241: 515-520.
17. Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. Endocr Rev. 1994; 15: 555-573.
18. Ikeo S, Yamauchi K, Shgematsu S, et al. Differential effects of growth hormone and insulin-like growth factor I on human endothelial cell migration. Am J Physiol Cell Physiol 2001; 280: 1255-1261.
19. Evans LM, Davies JS, Goodfellow J, et al. Endothelial dysfunction in hypopituitary adults with growth hormone deficiency. Clin Endocrinol (Oxf). 1999; 50: 457-464.
20. Cittadini A, Guocolo A, Merola B, et al. Impaired cardiac performance in growth hormone deficient adults and its improvment after growth hormone replacement. Am J Physiol. 1994; 267: E 219.
21. Levenson J, Simon AC, Cambien FA, Beretti C. Cigarette smoking and hypertension. Factors independently associated with blood hyperviscosity and arterial rigidity. Arteriosclerosis. 1987; 7: 572-577.
22. Obuobie K, Smith J, Evans LM, et al. Increased central arterial stiffness in hypothyroidism. J Clin Endocrinol Metab. 2002; 87: 4662-4666.
23. Dart AM, Lacombe F, Yeoh JK, et al. Aortic distensibility in patients with isolated hypecholesteolaemia, coronary artery disease or cardiac transplantation. Lancet. 1991; 338: 270-273.
24. Twardowski R, Mandecki T, Mizia-Stec K, et al. Znaczenie hormonu wzrostu w patogenezie chorób układu sercowo-naczyniowego. Pol Arch Med Wewn. 2002; 108: 925-929.
25. Colao A, Spiezia S, Di Somma C, et al. Circulating insulin-like growth factor-I levels are correlated with the atherosclerotic profile in healthy subjects independently of age. J Endocrinol Invest. 2005; 28: 440-448.
26. Chisalita SI, Nitert MD, Arnqvist HJ. Characterisation of receptors for IGF-I and insulin; evidence for hybrid insulin/IGF-I receptor in human coronary artery endothelial cells. Growth Horm IGF Res. 2006; 16: 258-266.