CLINICAL STUDY

Relation of left ventricular hypertrophy to cardiovascular complications in diabetic hypertensives

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Abstract

The presence of diabetes mellitus and other risk factors of atherosclerosis, such as obesity, smoking and hyperlipidemia, in hypertensive patients makes the prognosis worse. Authors compared the clinical findings in diabetic hypertensive patients with and without left ventricular hypertrophy, the presence of which was diagnosed and defined by echocardiography.

The study is based on the analysis of hospital records of 115 hypertensive patients treated at our department during the period 1998—1999. Left ventricular hypertrophy (LVH) was defined by echocardiography as left ventricular mass index >134 g/m^2 in men and >110 g/m^2 in women. Left ventricular hypertrophy was found in 79 patients (mean age 64.6 ys) but not in 36 patients (mean age 63.3 ys). Both groups were matched as to age and sex, intensity and duration of hypertension and diabetes, obesity, smoking and hyperlipidemia.

In LVH-positive patients, there was a statistically significant incidence of heart failure, mitral regurgitation and renal involvement and a more non-significant incidence of left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation and stroke than in LVH-negative ones.

Left ventricular hypertrophy usually complicates the course of hypertension. Authors recommend to investigate the presence of left ventricular hypertrophy in hypertensives as it carries a much more complicated course of the disease. ***(Tab. 5, Ref. 28.)***

Key words: left ventricular hypertrophy, arterial hypertension, diabetes mellitus, cardiovascular complication, risk factors.

Arterial hypertension (HTN) is an important factor for the development of left ventricular hypertrophy LVH ischaemic heart disease, heart failure and many other cardiovascular and non-cardiovascular diseases (25). In addition to arterial hypertension, there are also other metabolic diseases, which we categorize among risk factors for atherosclerosis development such as: diabetes mellitus (DM), overweight and obesity (body mass index (BMI) >27 kg/m^2) and hyperlipidemia. These risk factors contribute to an increase in the incidence of cardiovascular changes such as left ventricular hypertrophy and other organs changes, including their dysfunction or failure, through their direct effect or through increasing blood pressure itself (10, 23, 27).

For a long period of time it was known that there is a strong relationship between hypertension, diabetes milletus, and hyperinsulinism in obese diabetics as it is in obese non-diabetics. Some studies have shown a direct relationship between hyperinsulinism and blood pressure (27). So the presence of diabetes in hypertensives represents an additional independent risk factor to them.

At the beginning left ventricular hypertrophy is an adaptive response to chronic pressure and volume overload. This mechanism of adaptation normalizes left ventricular stress in patient's heart, but after a prolonged period of time, it becomes maladaptive. LVH then becomes an independent risk factor for

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increased cardiovascular and non-cardiovascular events in hypertensives (9, 18).

Framingham study demonstrated that higher occurrence with hypertension, diabetes mellitus and obesity (15). Some further clinical studies demonstrated that diabetic patients have a bigger mass of left ventricle and a bigger thickness of left ventricular walls in comparison with nondiabetic patients (20, 24).

Our study target was to compare the presence of serious clinical events and complications such as heart failure, left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation, mitral regurgitation, renal involvement and stroke in diabetic hypertensive patients with LVH with those without it.

Patients and methods

Patients

We analysed hospital records of hospitalised patients in our department during the time-period 1998—1999. Most common reasons for hospitalisation were worsening of cardiac heart failure, myocardial infarction, arrhythmias, stroke, worsening of hypertension (such as hypertensive crisis) or uncontrolled diabetes mellitus. Some of the admitted patients had more than one reason for their admission.

All these patients were well examined also by echocardiography. Out of this set of patients we found 115 diabetic hypertensives (56 males, 59 females), out of whom 79 patients (36 males, 43 females, average age 64.6±9.8 ys, range 37—80 ys) had LVH and 36 patients (20 males, 16 females, average age 63.3±10.3 ys, range 41—85 ys) did not have it (Tab. 1).

Tab. 1. Characteristics of diabetic hypertensives with and without left ventricular hypertrophy.

Hypertension+diabetes mellitus	LVH+	LVH-	Statistical significance
Total number of patients	79	36	
Men (%)	36 (46)	20 (56)	NS
Women (%)	43 (54)	16 (44)	NS
Age (y)	64.6±9.8 (37-80)	63.3±10.3 (41-85)	NS
Duration of AH (y)	12.1±6.5	12.0±6.2	NS
Duration of DM (y)	10.2±6.9	10.3±6.6	NS
SBP (mmHg)	155.2±14.9	153.3±17.9	NS
DBP (mmHg)	88.2±8.7	89.0±11.1	NS
LVM (g)	308.8±60.2	206.1±43.8	p<0.001
LVMI (g/m^2)	162.5±24.8	107.2±17.5	p<0.001
BSA (m^2)	1.90±0.19	1.91±0.17	NS
IVSd (mm)	12.3±1.6	10.7±1.5	p<0.001
LVPWd (mm)	11.5±1.6	10.0±1.6	p<0.001
LVIDd (mm)	53.5±5.6	47.5±4.8	p<0.001
Left atrium (mm)	42.9±4.3	38.8±4.0	p<0.001
BMI (kg/m^2)	28.6±3.7	27.8±3.7	NS
EF (%)	46.9±10.6	56.7±7.2	p<0.001
Mean of blood glucose level (mmol/l)	8.3±2.2	9.3±2.9	p<0.05

SBP: Systolic blood pressure, DBP: diastolic blood pressure, LVM: left ventricular mass, LVMI: left ventricular mass index, BSA: body surface area, IVSd: thickness of interventricular septum in diastole, LVIDd: left ventricular internal diameter in diastole, LVPWDd: left ventricular posterior wall in diastole, BMI: body mass index, EF: ejection fraction. p<0.05: significant (S), p>0.05: nonsignificant (NS)

Methods

Echocardiography

Patients were examined in supine position on their left side. Examination was performed by a 2-dimensional guided M-mode approach. Left ventricular hypertrophy was defined according to Penn convention while calculating LVH (7). The ventricular size of these patients was within the normal range. Patients with distorted shape of ventricles or with low quality views were excluded from our analysis. We judged the presence of LVH by echocardiography according to the following formula (3, 4):

$$LVM_{(g)} = 1.04 \times [(IVSd + LVIDd + LVPWd)^3 - (LVIDd)^3] - 13.6$$

$LVM_{(g)}$ = left ventricular mass in grams, IVSd = thickness of interventricular septum in diastole, in cm, LVIDd = left ventricular internal diameter in diastole, in cm, LVPWd = left ventricular posterior wall in diastole, in cm. By adjusting LVM (left ventricular mass) to body surface area we calculated left ventricular mass index (LVMI) and so we could define the presence of LVH. If LVMI was >134 g/m^2 in men or >110 g/m^2 in women, LVH was considered as being present (5, 6, 7).

Risk factors

Diabetes mellitus was defined by history taking, medical documents and/or at least by measuring fasting blood glucose twice (≥7 mmol/l) or by oGTT (oral glucose tolerance test) with blood glucose level of ≥11.1 mmol/l in the second hour (120 min) after oral glucose intake of 75 g glucose load.

Overweight and obesity were defined according to BMI body mass index. They were considered as positive, if BMI >27 kg/m^2.

Hypercholesterolemia was defined according to total blood cholesterol. A level >5.2 mmol/l was considered as abnormal. Hypertriglyceridemia, if the level of triglycerides in the blood was >2.1 mmol/l. Increased level of LDL was considered if it was >3.5 mmol/l and a level of HDL lower than <0.9 mmol/l was considered as abnormal.

Smoking was judged by history taking.

We measured arterial blood pressure (systolic and diastolic) by standard sphygmomanometer method (first and fifth Korotkov sounds). We calculated the average of several readings along five consecutive days. These patients were on anti-hypertensive treatment.

Clinical events, diseases and finding

(a) The presence of systolic heart failure was defined by history taking, physical examination and X-ray findings in addition to ECHO results (ejection fraction (EF) ≤40 %), supported by the improvement noticed in the condition of a given patient after administrating the standard treatment of heart failure. Ejection fraction was defined by M-mode ECHO where examinations (at least three) were performed by an experienced cardiologist. Each

results got were compared and adjusted to an experienced subjective visual evaluation. The ellipsoidal model by Teichholz was used to help in detecting EF with accuracy. So, the following formula was utilized:

$V = [7.0 \div (2.4 + D)] D^3$,

where V is the volume of left ventricle and D is left ventricular internal dimension determined by ECHO. In case of abnormal kinesis in the apical region or other regions of left ventricle, EF was corrected by visual examination of an experienced echo cardiographer.

(b) The presence of left ventricular diastolic dysfunction was judged as above but with normal EF (EF>45 %). The presence of sample volume was positioned at the level of tips of mitral leaflets. The mean of three revolutions was calculated. A typical picture of diastolic dysfunction (in case of sinus rhythm) was a transmitral dopplerogram with the A peak higher than E peak, „pseudonormal pattern" (peak E higher than peak A but with shortened deceleration time). We put attention also to a „restrictive pattern".

(c) Occurrence of myocardial infarction was defined by typical ECG findings and/or positive medical documents.

(d) The presence of chronic atrial fibrillation was found out from medical documents and was supported by at least four ECGs performed during a period of two weeks.

(e) The presence of mitral regurgitation was judged by ECHO-doppler examination.

(f) Serum creatinine was considered as a parameter of renal involvement (serum creatinine was measured twice in a two weeks interval, the average of which was calculated). Level of serum creatinine >120 μmol/l was considered as abnormal.

(g) Stroke was diagnosed and documented by a neurologist.

Statistical analysis

Differences in the prevalence of individual cardiovascular events and diseases heart failure, left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation, mitral regurgitation, renal involvement and stroke in hypertensives with LVH against hypertensives without LVH were calculated by the help of contingent tables 2x2 with the use of testing character chi^2 (chi-square difference). Characteristics of groups (mean values and standard deviations) were compared by t-test (Student's test) on the basis of different values of significance. Calculations were done by statistical program "Primer of Biostatistics" (22).

Results

Both compared groups of diabetic patients (hypertensives with and without LVH) did not have significant differences in demographic data. Even though females were more prevalent in the group of hypertensives without LVH and males were more common in the group of hypertensives with LVH, these differences did not reach statistical significance. The duration of hypertension and diabetes mellitus was statistically not significant in both compared groups of diabetic hypertensives. Diabetic hypertensives (with and without LVH) did not have differences in the mean values of treated blood pressure during hospitalisation. Diabetic hypertensives with LVH had in comparison with the group of diabetic hypertensives without LVH a bigger dimension of the left ventricle (in end-diastole) and a bigger dimension of the left atrium both statistically significant. Ejection fraction was lower in the group of diabetic hypertensives with LVH than that in the group of diabetic hypertensives without LVH (statistically significant) (Tab. 1). Diabetic hypertensives with LVH used more (statistically nonsignificant) ACE inhibitors and diuretics (Tab. 2). A bigger percentage of diabetic hypertensives without LVH was without antihypertensive treatment (statistically significant) and on the contrary hypertensives with LVH were more often treated with combined antihypertensive drugs (statistically nonsignificant) (Tab. 3). Both groups of hypertensives showed non-significant differences in the antidiabetic treatment (Tab. 2). Both groups of hypertensives showed non-significant differences in the presence or absence of atherosclerotic risk factors such as overweight and obesity, hypercholesterolemia, hypertriglyceridemia increased level of LDL, decreased level of HDL and of smoking habit (Tab. 4.)

The occurrence of clinical events such as heart failure, mitral regurgitation and renal involvement was significantly more

Tab. 2. Antihypertensive and antidiabetic treatment in diabetic hypertensives with and without LVH.

Treatments	Hypertension+diabetes				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
HTN, ACE inhibitors	57	72.2	19	52.8	NS
HTN, Betablockers	27	34.2	10	27.8	NS
HTN, Calcium antagonists	32	40.5	16	44.4	NS
HTN, Diuretics	39	49.4	8	22.2	NS
Diabetics on diet	10	12.7	9	25.0	NS
Diabetics on oral hypoglycaemic agents	58	73.4	20	55.5	NS
Diabetics on insulin	19	24.1	10	27.8	NS

p<0.05: significant (S), p>0.05: nonsignificant (NS)

Tab. 3. Intensity of anti-hypertensive treatment in hypertensives with and without LVH.

Antihypertensive treatment	Hypertension				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
Without therapy	1	1.3	7	19.4	p<0.005
Monotherapy	25	31.6	10	27.8	NS
Combined therapy 2 drugs	32	40.5	14	38.9	NS
Combined therapy 3 drugs	18	22.8	51	3.9	NS
Combined therapy 4 drugs	3	3.8	0	0	NS

p<0.05: significant (S), p>0.05: nonsignificant (NS)

Tab. 4. Occurrence of other atherosclerotic risk factors in hypertensives with and without LVH.

Risk factors	Hypertension+diabetes				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
Overweight and obesity	51	64.6	20	55.6	NS
Hypercholesterolemia	26	32.9	15	41.7	NS
Hypertriglyceridemia	22	27.8	14	38.9	NS
Decreased level of HDL	29	36.7	11	30.6	NS
Increased level of LDL	12	15.2	6	16.7	NS
Smoking	19	24.1	10	27.8	NS

p<0.05: significant (S), p>0.05: nonsignificant (NS)

Tab. 5. Occurrence of cardiovascular events and diseases in hypertensives with and without LVH.

Cardiovascular events and diseases	Hypertension+diabetes				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
Heart failure	41	51.9	3	8.3	p<0.003
LV diastolic dysfunction	36	45.6	10	27.8	NS
Myocardial infarction	45	57.0	12	33.3	NS
Chronic atrial fibrillation	17	21.5	4	11.1	NS
Mitral regurgitation	40	50.6	4	11.1	p<0.007
Renal involvement	31	39.2	4	11.1	p<0.035
Stroke	16	20.3	6	16.6	NS

LV: left ventricular, p<0.05: significant (S), p>0.05: nonsignificant (NS)

common in diabetic hypertensives with LVH than in diabetic hypertensives without LVH (Tab. 5). Incidence of left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation and stroke were more common in diabetic hypertensives with LVH than in diabetic hypertensives without LVH, these differences did not reach statistical significance (Tab. 5).

Discussion

Left ventricular hypertrophy when accompanies hypertension, carries an increase in mortality and morbidity (11, 27). The presence of other atherosclerotic risk factors as diabetes mellitus, obesity, and hypercholestrolaemia worsens the prognosis in these patients (12, 13). That is why we have looked for the increase in morbidity among hypertensive diabetics when LVH is proved in our patients. In our group of patients there were no differences in demographic parameters among hypertensive diabetics with LVH when compared with those without hypertrophy. We had a non-significant increase in the number of females enrolled in our comparison in the group of patient with LVH (Tab. 1). This stresses a higher prevalence of obesity and diabetes mellitus in females in addition to the role of (metabolic syndrome) in the development of left ventricular hypertrophy. The duration of hypertension was not different in both groups (Tab. 1). We have expected to have a longer duration of hypertension in the group of patients with LVH. It has to be mentioned here that by history alone it is difficult to define the exact duration of hypertension since this disease is not accompanied with symptoms in many patients in its early course. It is common that patients seek the help of their doctors because of other problems so hypertension in them is discovered accidentally. On the other hand the development of left ventricular hypertrophy does not depend only on the duration of hypertension since other factors as genetic predisposition play their own role (17). It is logical to expect higher readings of hypertension in hypertensive diabetics with LVH than those without it. But in our patients there were no differences in blood pressure readings (during the day) among both groups (Tab. 1). This could be a result of the intensive treatment given to the patients with LVH. The optimal systolic and diastolic blood pressures were not reached in our patients this could be due to the fear of exposing them to the risk of orthostatic hypotension. Both groups of patients had approximately the same duration of diabetes mellitus, but the average blood glucose level was significantly higher in those patients without LVH (Tab. 1). ACEI and diuretics have been used more frequently (non-significant difference) in patients with LVH. This also reflects the presence of a severer form of the disease in these patients as it is seen that the incidence of heart failure among them is higher (Tab. 2). So the use of effective treatment in our patients as ACEI had also the target of regressing left ventricular hypertrophy. The use of other anti-hypertensive agents was not different in both groups. In fact some patients without LVH (the milder form of hypertension) were not receiving any anti-hypertensive treatment. The use of combined anti-hypertensive treatment was more frequently noticed in those patients with LVH (Tab. 3). Also the use of many anti-hypertensive drugs reflects the fact that hypertensives with LVH suffer from a severer form of the disease. In our diabetic hypertensive patients there was a trend (non-significant difference) towards more obesity when LVH was present (Tab. 4). Whereas the incidence hypercholestrolemia and hypertriglyceridemia was non-significantly lower (Tab. 4).

The incidence of symptomatic and nonsymptomatic heart failure (systolic and diastolic), mitral regurgitation and renal dysfunction was significantly higher when left ventricular hypertrophy accompanied hypertension (Tab. 5).

It is worth noting that we did not find out a statistically significant increase in the incidence of diastolic dysfunction of left ventricle, myocardial infarction, chronic atrial fibrillation and strokes in those hypertensive diabetics with LVH than in diabetic hypertensives without LVH (Tab. 5).

There is a stronge relation between hypertension and diabetes mellitus type II, where both diseases take part in the development of left ventricular hypertrophy, representing independent risk factors for many cardiovascular and non-cardiovascular events, so increasing morbidity and mortality in the involved patients (14, 19).

Beside diabetes mellitus other pathogenic factors play their role in the abnormality of left ventricular function, vascular system and other organs. As hypertension increases the mass of left ventricle there is also the effect of some growth hormones on the heart (e.g. insulin like growth factor — IGF) which can lead to an increase in the mass of left ventricle by depositing more collagen in its interstitium besides its deposition in the perivascular space. Further there is an increase in the amount of cardiac sorbitol in myocyts and interstitium and hypersensitivity of myocardium to Ca^{2+} with the increase of Ca^{2+} ATPase activity (16, 26).

Many clinical studies have shown that in diabetes type II, hypertension or hypertrophy of left ventricle the incidence of left ventricular dysfunction is high. The presence of significant interstitial fibrosis makes the process of chronic heart failure more common and quicker in diabetic hypertensives than in those normotensive diabetics or non-diabetic hypertensives (1, 19).

Insulin resistance is a prominent character in diabetes type II. The accompanying hyperinsulinemia has a great effect on kidneys (retention of sodium and water) the matter, which also leads to an increase in blood pressure. Hyperinsulinemia is common among obese diabetic hypertensives (DM II) and even in obese non-diabetic hypertensives. The activation of many hormones in hypertension, DM, or in their combination worsen the situation in these patients (renin—angiotensin—aldosterone system, insulin system, and atrial natriuretic system). In arterial hypertension the occurrence of hyperinsulinemia is possible independently of body weight or the presence of glucose intolerance so insulin sensitivity (the elevation in insulin resistance) is reduced more in obese hypertensives than in obese normotensives (8, 14). Bogalusa Heart study has proved a significant positive correlation between fasting insulinemia and readings of systolic and diastolic blood pressure. Isolated hyperinsulinemia can by sometimes the cause of hypertension (8, 14, 21, 26, 28).

Insulin resistance or hyperinsulinemia (which very commonly may accompany hypertension) can influence heart mass directly (by the effect of insulin on growth receptors) or indirectly by stimulating adrenergic tone (sympathetic nervous system) with the result of elevated blood pressure. The hypertrophic effect of insulin can by theoretically expressed as concentric remodeling or concentric hypertrophy of left ventricle (2).

The combination of arterial hypertension and diabetes can worsen cardiovascular mortality and morbidity to a higher extent than isolated hypertension or diabetes (26, 27).

We have analyzed the files of 115 hospitalized patients with hypertension and diabetes where we found out a higher incidence of heart failure, mitral regurgitation and renal dysfunction in the group of patients with left ventricular hypertrophy, in addition to a higher non-significant incidence in other complications as diastolic dysfunction of left ventricle, myocardial infarction, chronic atrial fibrillation and stroke.

We expect that intensive anti-hypertensive treatment and reaching regression of left ventricular hypertrophy has to be a therapeutic target of which we can expect a reduction in cardiovascular complications in hypertensive patients with diabetes. In this aspect the availability of echocardiographic examination is crucial.

References

1. Mogensen CE: Management of the diabetic patient with elevated blood pressure or renal disease. In: Laragh JH, Brenner BM (Eds): Hypertension. Pathophysiology, Diagnosis and Management. New York, Raven Press 1995; 2335 p.

2. Costa CHRM, Batista MC, Moises VA et al: Serum insulin levels, 24-hour blood pressure profile, and left ventricular mass in nonobese hypertensive patients. Hypertension 1995; 26 (2): 1085—1088.

3. Devereux RB: Detection of left ventricular hyper-trophy by M-mode echocardiography. Anatomic validation, standardization and comparison to other methods. Hypertension 1987; 2 (Suppl II): II.19—II.26.

4. Devereux RB, Alonso RD, Lutas EM et al: Echo-cardiographic assessment of left ventricular hyper-trophy: comparison to necropsy finding. Amer J Cardiol 1986; 57: 450—458.

5. Devereux RB, Koren MJ, DeSimone G et al: Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. Europ Heart J 1993; 14 (Suppl D): 8—15.

6. Devereux RB, Roman MJ: Hypertensive cardiac hypertrophy: Pathophysiologic and clinical characteristics. Pp. 409—432 In: Laragh JH, Brenner BM (Eds): Hypertension. Pathophysiology, Diagnosis and Management. New York, Raven Press 1995, 3139 p.

7. Eagle KA, Blank DJ, Aguiar E et al: Economic impact of regression of left ventricular hypertrophy by antihypertensive drugs. J Human Hypertens 1993; 4: 341—351.

8. Ferrannini E: The phenomenon of insulin resistance: Its possible relevance to hypertensive disease. In: Laragh JH, Brenner BM (Eds): Hypertension. Pathophysiology, Diagnosis and Management. New York, Raven Press 1995, 2281 p.

9. Ghanem Wisam MA, Murín J, Bulas J et al: Left ventricular hypertrophy in hypertensives. Bratisl Lek Listy 2000; 1018: 455—459.

10. Ghanem Wisam MA, Murín J, Bulas J: Significance of left ventricular hypertrophy in hypertensives. Vnitř Lék 1998; 9: 513—517.

11. Gregor P, Špaček R, Widimský P: Hypertrofie myokardu příčiny, diagnostika a léčba u různych stavů. Nonivas Cardiol 1996; 5 (Suppl 2): 81—87.

12. Hense WH, Gneiting B, Muscholl M et al: The associations of body size and body composition with left ventricular mass: Impact for indexation in adults. J Amer Coll Cardiol 1998; 32: 451—457.

13. Himeno E, Nishino K, Okazaki T et al: A weight reduction and weight maintenance program with long-lasting improvement in left ventricular mass and blood pressure. J Amer Hypertens 1999; 12: 682—690.

14. Hirofumi T, Nobutaka D, Toshio K et al: The relationship of hyperinsulinemic state to left ventricular hypertrophy, microalbuminuria, and physical fitness in borderline and mild hypertension. Amer J Hypertens 1997; 10: 587—591.

15. Kannel WB, McGee DL: Diabetes and cardiovascular risk factors: The Framingham Heart Study. Circulation 1979; 59: 8—13.

16. Kenneth RC, Grace AA: Principles of cardiovascular molecular and cellular biology. Pp. 1624—1649. In: Braunwald E (Ed): Heart disease. 5th edition. W.B. Saunders comp. 1997; Chapter 48.

17. Kim Hyo-Soo, Lee Myoung-Mook, Oh Byung-Hee et al: Synergistic effect of angiotensin-converting enzyme and angiotensinogen gene on cardiac hypertrophy. Internat J Cardiol 2000; 72: 151—161.

18. Murín J: Remodelácia srdca a ciev. Bratislava, SAP 1997, 103 p.

19. Stern N, Tuck ML: Pathogenesis of hypertension in diabetes mellitus. In: Laragh JH, Brenner MB (Eds): Hypertension. Pathophysiology, Diagnosis and Management. New York, Raven Press 1995, 2301 p.

20. Nielsen FS, Ali S, Rossing P et al: Left ventricular hypertrophy in non-insulin-dependent diabetic patients with and without diabetic nephropathy. Diabet Med 1997; 14: 538—546.

21. Brownsey RW, Boone AN, Allard MF: Actions of insulin on the mammalian heart, pathology and biochemical mechanisms. Cardiovasc Res 1997; 34: 3—24.

22. Glantz SA: Primer of biostatistics. 4th edition. New York McGraw-Hill 1997, 491 p.

23. Strauer BE, Schwartzkopff B: Left ventricular hypertrophy and coronary microcirculation in hypertensive heart disease. Blood Press 1997; 6 (Suppl 2): 6—12.

24. Vanninen E, Mustonen J, Vainio P et al: Left ventricular function and dimensions in newly diagnosed non-insulin-dependent diabetes mellitus. Amer J Cardiol 1992; 70: 371—378.

25. Widimský J: Hypertrofie srdeční při hypertenzi — její klinický význam a možnosti jejího ovlivnění. Cor Vasa 1993; 35 2: 84—89.

26. Williams GH, Lilly LS, Seely EW: The heart in endocrine and nutritional disorders. Pp. 1887—1913. In: Braunwald E (Ed): Heart disease. 5th edition. W.B. Saunders comp. 1997; Chapter 61.

27. Wilson SC, Braunwald E: Pathophysiology of heart failure. Pp. 394—420. In: Braunwald E (Ed): Heart disease. 5th edition. W.B. Saunders comp. 1997; Chapter 61.

28. Yukihiko M, Yoshihiko S, Fumitaka O et al: Maternally transmitted susceptibility to non-insulin-diabetes mellitus and left ventricular hypertrophy. J Amer Coll Cardiol 1999; 33: 1372—1378.

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