Insertion/deletion polymorphism of angiotensin I converting enzyme gene and left ventricular hypertrophy in patients with type 2 diabetes mellitus

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Abstract

Introduction: Left ventricular hypertrophy (LVH) is a well known risk factor of death from cardiovascular causes. Patients with type 2 diabetes mellitus are at particularly high risk of developing cardiovascular disease, which accounts for 80% of deaths in this group. Type 2 diabetes mellitus is probably related to increased left ventricular mass (LVM). Existing data show that the renin-angiotensin-aldosterone (RAA) system may play a role in the development of LVH. Since the I/D polymorphism of angiotensin-converting enzyme (ACE) gene influences the activity of RAA, it is likely that it could also have an impact on LVH.

Aim: To assess the relationship between I/D polymorphism of the ACE gene and the severity of LVH assessed by echocardiography (Echo) in patients with type 2 diabetes mellitus.

Methods: The study group consisted of 103 patients (37 women and 66 men; mean age 60.1±9.1 years) suffering from type 2 diabetes mellitus with a mean duration of 9.0±6.5 years. BMI, waist-to-hip ratio (WHR), arterial blood pressure, LVM and LVM index (LVM indexed for body surface area [g/m^2] or height raised to the power 2.7 [$g/m^{2.7}$]) were evaluated. I/D polymorphism of the ACE gene was determined using polymerase chain reaction (PCR).

Results: Distribution of I/D polymorphism of the ACE gene in the study group was as follows: genotype II – 32.0%, ID – 42.7%, DD – 25.2% of patients. LVH was diagnosed in 43-71% of patients (depending on criteria used). Distribution of individual genotypes was similar in patients with and without LVH. Genotypes II, ID and DD were observed in 37.3%, 31.4% and 31.4% of patients without LVH (according to the Levy criteria) and in 26.9%, 53.9%, 19.2% in the LVH group, respectively. In persons with DD genotype, when compared to group II, significantly higher values of systolic and diastolic blood pressure were noted (147.7±20.2 *vs* 138.2±16.7 mmHg, p=0.03 and 89.4±9.7 *vs* 81.9±8.7 mmHg, p=0.004, respectively).

Conclusions: In patients with type 2 diabetes mellitus there is no relationship between I/D polymorphism of the ACE gene and LVH.

Key words: type 2 diabetes mellitus, left ventricular hypertrophy, ACE, polymorphism, genetics

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Introduction

Epidemiological studies consistently show that left ventricular mass (LVM) or hypertrophy (LVH) are important factors of cardiovascular morbidity and mortality [1-4]. Arrhythmias, impaired coronary flow reserve and disturbances of coronary flow regulation have often been observed among individuals with LVH.

Patients with type 2 diabetes mellitus are at particularly high risk of developing cardiovascular disease, which accounts for 80% of deaths in this group

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[6]. There are a few data concerning the incidence of LVH in these patients. However, it seems that type 2 diabetes mellitus might be associated with increased LVM, especially among women [7].

The discovery of the cardiac renin-angiotensin-aldosterone system (RAA) and the ability of angiotensin II to promote cardiomyocyte and fibroblast growth and the effectiveness of ACE inhibitors in hypertrophy regression suggest its contribution to cardiac hypertrophy development [1]. Activity of angiotensin I converting enzyme is an important regulating mechanism of the RAA system. The polymorphism within intron 16, characterised by the presence (insertion - I) or the absence (deletion – D) of 287-base pair, is important from the clinical point of view. It results in the following three genotypes: homozygotes II and DD and heterozygote ID.

It has been observed that DD homozygotes have the highest activity of plasma and tissue ACE, while II homozygotes have the lowest activity and heterozygotes ID are characterised by intermediate activity [8-11]. It is suggested that insertion could reduce gene expression. Thus there is an emerging question about the relationship between I/D polymorphism and LVH.

Previous studies have not provided an unequivocal results. Some authors have shown that allele D had a significant impact either on patients with hypertension [12-14] or without it [12, 15, 16]; however, these relationships could not be confirmed by other authors [15, 17]. The aim of the study was to assess the relationship between I/D polymorphism of angiotesin I convertase gene and the severity of LVH assessed by echocardiography (Echo) in patients with type 2 diabetes mellitus.

Methods

Patients

The study population consisted of 103 patients aged 36-79 years (mean 60.1±9.1 years) suffering from type 2 diabetes mellitus, with body mass index (BMI) ranging from 22.4 to 52.8 kg/m^2 (mean 31.5±5.2 kg/m^2). The study group included 37 women aged 42-76 years (mean 59.8±9.5 years) with BMI ranging from 25.1 to 45.7 kg/m^2 (mean 33.4±5.6 kg/m^2) with diabetes lasting for 1 to 27 years (mean 9.6±6.4 years) and 66 men aged 36-79 years (mean 60.2±9.0 years) with BMI between 22.4 and 52.8 kg/m^2 (mean 30.4±4.8 kg/m^2) and diabetes lasting for 0.5 to 32 years (mean 8.8±6.9 years). All study subjects were typical patients of a diabetes outpatient clinic with very different times of diabetes duration. All persons were treated with medical nutrition therapy and/or oral antiglycemic agents only.

The study was approved by the Ethics Committee. After obtaining informed consent from each patient, medical history was taken and physical examination including BMI, waist-to-hip ratio (WHR) and repeated measurement of blood pressure were performed.

Echocardiography

Echocardiography was performed in each patient by a cardiologist. During the examination wall thickness and contractility, expressed as LV ejection fraction (LVEF), were measured. The LVM was calculated based on LV diameter and wall thickness. The calculations were made according to the guidelines of the American Association of Echocardiography using the formula with the Devereux modification [19]: LVM=0.8 x {1.04 x [$(IVS_d+LVID_d+PTW_d)^3$-$LVID_d^3$]} +0.6, where LVM is left ventricular mass (grams), IVS_d is interventricular septum in diastole, $LVID_d$ is left ventricular internal diameter in diastole, and PTW_d is posterior wall thickness in diastole. Finally, LVH was assessed based on LVM index, LVM(c), where LVM was indexed for body surface area or height raised to the power 2.

The presence of LVH was analysed based on several criteria. According to Levy and the Framingham Study LVH was defined as LVM(c) ≥131 g/m^2 in men and ≥110 g/m^2 in women [20]. According to the European Society of Cardiology Guidelines from 2003 [21] the cut-off values for LVM (c) were set at ≥125 g/m^2 for men and ≥110 g/m^2 for women. According to the criteria of de Simone et al. [22] LVH was diagnosed based on the formula: LVM index/height raised to the power 2.7 with the values ≥50g/m$^{2.7}$ in men and ≥47 g/m$^{2.7}$ in women.

Genetics

The I/D ACE gene polymorphism was assessed using polymerase chain reaction (PCR). Genomic DNA was extracted from leucocytes using a non-enzymatic and non-organic method with the use of 2% Triton X-100 (LAH). The ACE I/D polymorphisms were detected by DNA amplification in polymerase chain reaction applying a pair of ACE 12 oligonucleotides as the specific primers: sense-5'-GCCCTGCAGGTGTCTGCAGCATGT-3' and antisense-5'--GGATGGCTCTCCCCGCCTTGTCTC-3' (LIND). The PCR products with these primers are DNA fragments: 319 base pair (bp) for allele D and 597 bp for allele I. Patients found to have DD genotype (homozygotes) were verified by the second run of PCR with a pair of ACE 34 oligonucleotides: 5'-TGGGACCACAGCGCCCGCCACTAC-3' as a sense primer and 5'-TCGCCAGCCCTCCCATGCCCATAA-3' as an antisense primer. This second pair of primers is specific for allele I (LIND) [23].

Statistical analysis

Relations between nominal variables (e.g. ACE genotype, sex, presence of hypertension) were analysed by the chi-square test or exact Fisher test for

dichotomous variables. The Hardy-Weinberg equilibrium for ACE genotype distribution was tested by the chi-square test. Since most of the variables were not distributed normally (Shapiro-Wilk test), nonparametric tests had to be applied. Between-group differences were analysed by Mann-Whitney U test and in multiple group analysis Kruskal-Wallis ANOVA was applied. Statistical significance was set at $p < 0.05$. Continuous variables are presented as mean ±SD. Statistical analyses were performed using "Statistica 6.1 Pl" software.

Results

Distribution of I/D polymorphism of the ACE gene in the study group was in Hardy-Weinberg equilibrium (p=0.19) and presented as follows: II genotype – 33 (32.0%) patients, ID genotype – 44 (42.7%) patients, DD genotype – 26 (25.2%) patients. After analysis of the frequency of alleles I and D, similar occurrence of allele D was found in men and women (52.6% and 43.6%, respectively).

Table I. ACE gene I/D polymorphism and studied parameters

	Whole group	ID	II	DD	p
	n=103	n=44	n=33	n=26	
Age [years]	60.1±9.1	60.6±10.2	59.4±8.1	60.2±8.6	NS
Females/Males	37/66	11/33	12/21	14/12	NS
Duration of diabetes [years]	9.0±6.5	8.2±5.8	9.9±7.0	9.1±6.9	NS
Hypertension [%]	81.6	81.8	75.8	80.8	NS
Duration of hypertension [years]	10.7±6.9	10.5±6.8	11.1±6.8	10.5±7.3	NS
BMI [kg/m^2]	31.5±5.2	30.7±4.1	31.8±5.9	32.5±6.1	NS
Obesity (BMI ≥30) [%]	57.3	59.1	54.6	57.7	NS
WHR	0.98±0.07	0.99±0.07	0.98±0.07	0.97±0.08	NS
Systolic Blood Pressure [mmHg]	142.7±18.8	143.2±19.1	138.2±16.7	147.7±20.2	*p=0.03
Diastolic Blood Pressure [mmHg]	84.8±10.2	84.3±10.9	81.9±8.7	89.4±9.7	*p=0.004
Echocardiographic parameters					
LA [cm]	4.15±0.52	4.11±0.47	4.26±0.52	4.10±0.59	NS
LVESD [cm]	3.30±0.82	3.25±0.77	3.41±0.93	3.23±0.77	NS
LVEDD [cm]	4.97±0.72	4.85±0.73	5.17±0.70	4.92±0.70	NS
LVPWs [cm]	1.60±0.35	1.58±0.39	1.62±0.31	1.61±0.36	NS
LVPWd [cm]	1.13±0.22	1.14±0.23	1.12±0.21	1.11±0.23	NS
IVSs [cm]	1.76±0.32	1.83±0.34	1.73±0.30	1.69±0.30	NS
IVSd [cm]	1.27±0.25	1.31±0.28	1.22±0.19	1.26±0.25	NS
IVS/LVPW	1.15±0.36	1.19±0.43	1.10±0.28	1.15±0.34	NS
LVM [g]	240.4±79.85	235.0±78.0	251.5±88.7	235.6±72.3	NS
LVM(c) [g/m^2]	122.8±38.1	118.6±36.6	129.2±44.9	122.0±30.6	NS
LVM(c) [g/m$^{2.7}$]	60.0±19.4	57.8±20.5	62.1±20.1	63.2±17.4	NS
LVEF [%]	55.06±10.67	54.5±10.6	55.8±12.1	55.0±9.1	NS
LVH					
Levy et al. criteria [20] [n/%]	51 (49.5%)	16 (31.4%)	19 (37.2%)	16 (31.4%)	NS
ESC criteria [21] [n/%]	45 (43.7%)	17 (37.8%)	16 (35.5%)	12 (26.7%)	NS
de Simone et al. criteria [22] [n/%]	74 (71.8%)	27 (36.5%)	25 (33.8%)	22 (29.7%)	NS

** II vs DD*

Abbreviations: LVH – left ventricular hypertrophy, LA – left atrial dimension, LVEDD – left ventricular end diastolic dimension, LVESD – left ventricular end systolic dimension, LVPWs – left ventricular posterior wall systolic thickness, LVPWd – left ventricular posterior wall diastolic thickness, IVSs – interventricular septum systolic thickness, IVSd – interventricular septum systolic thickness, LVM – left ventricular mass, LVM(c) – left ventricular mass index, LVEF – left ventricular ejection fraction, BMI – body mass index, WHR – waist-to-hip ratio

Comparing the groups with II, ID and DD genotypes no significant differences were found regarding age, duration of diabetes, prevalence of hypertension and its duration, incidence of obesity, BMI and WHR values (Table I). In patients with DD genotype, when compared to the II group, significantly higher values of systolic blood pressure were observed. Analysis of the groups with DD, II and ID polymorphisms revealed no differences in echocardiographic parameters (Table I).

Using the criteria of Levy et al. [20] LVH was observed in 51 patients (49.5%) and were two times more frequent in women than in men (73.0% and 36.4% respectively; p=0.0005). Patients with LVH, compared to those without it, were slightly younger but they had a longer duration of hypertension and diabetes, higher BMI and higher values of systolic blood pressure. Analysis of the distribution of I/D polymorphism revealed no significant differences between these two groups. In the group, in which LVH was diagnosed according to the Levy criteria, the frequencies of II, ID and DD genotypes were similar (Figure 1). In the group without LVH there were also no differences in the genotype distribution (26.9%, 53.9% and 19.2%, respectively).

Applying boundary values of LV index according to the ESC guidelines, LVH was diagnosed in 45 patients (43.7%). In women the rate of LVH was 48.6%, whereas in men it reached 40.9% (NS). In the comparison of the two groups of patients with and without LVH no significant differences regarding age and duration of diabetes and hypertension were revealed. The groups did not differ significantly also when considering the distribution of ACE genotypes. In the LVH group similar frequencies of the II, ID and DD genotypes were observed.

According to the criteria of de Simone et al. [22] LVH was found in 74 (71.8%) patients, and it was significantly higher in women (86.5% *vs* 63.6%, p=0.02). Similarly as in the previous analyses patients with LVH were slightly younger with longer duration of diabetes and hypertension. Genotype distribution was not significantly different in persons with or without LVH (Figure 1).

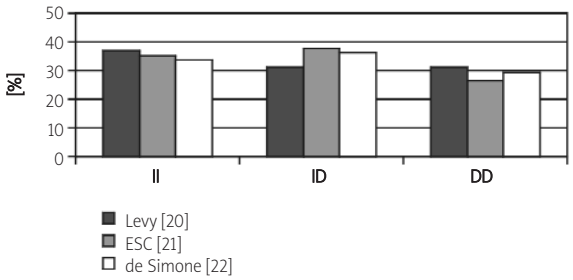

Figure 1. Prevalence of II, ID and DD genotypes in patients with left ventricular hypertrophy diagnosed based on different criteria

Discussion

Hypertrophy of the LV is an independent factor increasing the risk of death from cardiovascular causes. It seems that in persons with LVH, compared to individuals with systolic heart failure and multivessel ischaemic heart disease, such risk is even higher [24]. In the present study the influence of I/D polymorphism of the ACE gene on LVH was analysed. The frequency of diagnosed LVH was dependent on the criteria used. According to the standards from the Framingham study LVH was recognised in 49.5% of patients and it was significantly higher in women than in men (73% *vs* 36.4%). When the ESC and the European Society of Hypertension criteria were applied LVH was diagnosed in 43.7% of patients with similar incidence in women and men (48.6% and 40.9%). On the other hand, the use of criteria proposed by de Simone et al. implicated the diagnosis of LVH in 71.8% of patients and its incidence was significantly higher in women than in men (86.5% *vs* 63.6%, p=0.02). Similar results have been obtained by Dawson et al. [25] in a large group of 371 patients with type 2 diabetes mellitus. With the use of the Framingham criteria the authors observed the incidence of LVH in 42.9% of patients compared with 71.2% when the criteria of de Simone et al. [22] were applied. In the previously quoted Framingham study it was found that the prevalence of LVH diagnosed by echocardiography increases with age; from 8% in men aged under 30 years to 33% in men aged 70 years or more. LVH in women in the same age groups were 5% and 49% respectively. In our study, using Framingham criteria LVH was either often observed in women in whose mean age was 59.8±9.5 or was similar to men (60.1±9.0). In the study by Gladerisi et al. based on the Framingham population, LVM was higher in patients with type 2 diabetes mellitus compared to patients without diabetes, although statistical significance was reached only in women [7]. Higher incidence of LVH in women with type 2 diabetes mellitus could be the reason for the much higher risk of cardiovascular diseases and deaths when compared to men.

Irrespective of the criteria applied for LVH there was no association observed between LVM and I/D polymorphism of the ACE gene. Data from the studies addressing this issue are not consistent. Schunkert et al. observed the relationship between echcardiographically assessed LVH and the frequency of D allele either in persons with elevated or normal blood pressure [12]. A similar correlation was found by Iwai et al., which assessed LVH by echocardiography [13]. Different results were obtained by Kupari et al. and Calentano et al. [14, 15]. They came to the conclusion that in patients without additional cardiovascular risk factors (smoking, diabetes, hypercholesterolaemia) the frequency of LVH

was almost four times higher in persons with DD genotype when compared to the others (ID/II). However, with the coexistence of other risk factors that relationship disappeared. Estatio et al., in a group of 289 persons with type 2 diabetes mellitus, demonstrated that DD genotype was an independent risk factor of LVH [18]. Kuznetsova et al. in the metaanalysis from 2000 including 6000 subjects revealed significantly higher risk of LVH in DD homozygotes compared to II homozygotes [14]. The correlation was assessed, however, only in patients without antihypertensive therapy. In the work of the Japanese authors based on autopsy examination in 443 persons a significant relationship between DD genotype and heart mass was found, which was independent from the coexistence of hypertension [26].

These observations, however, are not confirmed by all other investigators. In the previously mentioned Framingham study, the influence of I/D polymorphism on LVH was analysed in a group of approximately 2500 persons excluding patients younger than 20 years, with the suspicion for congenital or acquired heart disease and with renal failure. There was no difference observed regarding LVM and the frequency of diagnosed LVH according to the different genotypes [27]. Also, no significant relationship between LVH and gene polymorphism was observed by Czarnecka et al., either in patients with hypertension or without it [17]. In the paper by Gruchała et al. the correlation between I/D polymorphism of the ACE gene and AT1 receptor and LVM was assessed [28]. The control group consisted of 360 persons with coronary heart disease confirmed by coronary angiography. Only the presence of DD and CC genotype was positively correlated with LVM, while no significant relationship between individual I/D polymorphism and LVH was observed.

Despite the theoretical predictions suggesting a possible relation between I/D polymorphism of the ACE gene and LVH, in the light of our study and large discrepancies found in other work addressing this problem, such a relation seems to be questionable. It might be possible that environmental risk factors and the therapy used could have a significant influence on this relation.

Conclusion

In patients with type 2 diabetes mellitus there is no relationship between I/D polymorphism of the ACE gene and left ventricular hypertrophy.

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Polimorfizm I/D genu enzymu konwertującego angiotensynę I a przerost mięśnia lewej komory u chorych na cukrzycę typu 2

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Streszczenie

Wstęp: Przerost lewej komory serca (LVH) jest uznanym czynnikiem ryzyka zgonu z przyczyn sercowo-naczyniowych. Grupę szczególnego ryzyka schorzeń układu krążenia stanowią chorzy z cukrzycą typu 2, u których 80% zgonów spowodowane jest chorobami tego układu. Wydaje się, że cukrzyca typu 2 wiąże się ze zwiększoną masą lewej komory (LVM). Istnieją dowody, iż układ renina-angiotensyna-aldosteron (RAA) może odgrywać rolę w rozwoju LVH. Ponieważ polimorfizm I/D genu konwertazy angiotensyny I (ACE) wpływa na aktywność układu RAA, prawdopodobny wydaje się także jego wpływ na LVH.

Cel: Ocena zależności między obecnością polimorfizmu I/D genu ACE a stopniem przerostu lewej komory mięśnia sercowego, ocenianego za pomocą ultrasonografii (UKG) u osób z cukrzycą typu 2.

Metodyka: Grupa badana: 103 osoby (37 kobiet i 66 mężczyzn) chore na cukrzycę typu 2, trwającą średnio 9,0±6,5 lat, w wieku średnio 60,1±9,1 lat. Oceniane parametry: BMI, wskaźnik talia/biodra (WHR), ciśnienie tętnicze, LVM oraz wskaźnik LVM [LVM odniesiona do powierzchni ciała (g/m^2) lub wzrostu podniesionego do potęgi 2,7 ($g/m^{2,7}$)]. Polimorfizm I/D genu ACE oznaczano metodą łańcuchowej reakcji polimerazy (PCR).

Wyniki: W badanej grupie rozkład polimorfizmu I/D genu ACE przedstawiał się następująco: genotyp II – 32,0%, ID – 42,7%, DD – 25,2% chorych. LVH rozpoznano u 43–71% chorych (w zależności od przyjętych kryteriów). Rozkład poszczególnych genotypów był podobny w grupie osób z LVH i bez LVH. W grupie z LVH (wg kryteriów Levy) genotypu II, ID oraz DD występowały odpowiednio u 37,3%, 31,4% i 31,4% badanych, a w grupie bez LVH odpowiednio u 26,9%, 53,9% i 19,2%. U osób z genotypem DD obserwowano istotnie większe, w porównaniu z grupą II, wartości ciśnienia tętniczego skurczowego (147,7±20,2 *vs* 138,2±16,7 mmHg, p=0,03) i rozkurczowego (89,4±9,7 *vs* 81,9±8,7 mmHg, p=0,004).

Wnioski: Polimorfizm I/D genu ACE u chorych z cukrzycą typu 2 nie wykazuje związku z LVH.

Słowa kluczowe: cukrzyca typu 2, przerost lewej komory, ACE, polimorfizm, genetyka

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