Combined influence of diabetes mellitus and obesity on left ventricle remodeling in hypertensive patients


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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words: essential hypertension, left ventricular remodeling, diabetes mellitus, obesity, myocardial hypertrophy.

The aim of the study was to evaluate the effect of type 2 diabetes mellitus (T2DM) and obesity influence on the left ventricular (LV) remodeling peculiarities in hypertensive patients.

Materials and methods. In total, 327 patients, aged 38–74 years, were comprehensively examined. The enrolled patients were divided into 4 groups in dependence of the presence of associated disease: the 1st group – n = 87 hypertensive patients with T2DM combined with obesity, the 2nd group – n = 71 hypertensive patient with T2DM and the 3rd group – n = 65 hypertensive patients with obesity; the comparison group consisted of 74 patients with essential hypertension (EH) but without obesity or diabetes.

Echocardiography was performed according to the standard method of H. Feigenbaum to estimate the LV parameters. HbA1c was determined by turbidimetric method. Serum glucose levels were determined by ELISA.

Results. When comparing the three patient groups with those who had only EH, the most significant influence was found in combined influence of T2DM and obesity on the development of unfavorable type of LV remodeling with values of χ² = 29.371 and Pearson’s contingency coefficient (C) – 0.393 (P < 0.05). The presence of concomitant T2DM without obesity had a significant moderate relationship with the development of unfavorable LV geometry, χ² = 11.029 and C = 0.266 (P < 0.05), which indicates a much smaller impact on the process compared to the polymorbid effect of T2DM with obesity. Comparison of patients with a combination of EH and obesity with those who had only EH did not show a significant effect of concomitant obesity on the development of unfavorable types of LV geometry with values of χ² and C: 0.529 and 0.062, respectively (P > 0.05).

Conclusions. Essential hypertension with type 2 diabetes mellitus and obesity polymorbidity, but not in combination with type 2 diabetes mellitus or obesity alone, has the most significant association with hypertrophic types of LV remodeling. The coexistence of type 2 diabetes mellitus and obesity in hypertensive patients leads to the development of predominantly LV concentric hypertrophy.
Сочетанное влияние сахарного диабета 2 типа и ожирения на ремоделирование левого желудочка у пациентов с гипертонической болезнью

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Цель работы – оценить влияние сахарного диабета (СД) 2 типа и ожирения на особенности ремоделирования левого желудочка у пациентов с гипертонической болезнью (ГБ).

Материалы и методы. Обследовали 327 пациентов в возрасте 38–74 года. Пациентов поделили на 4 группы в зависимости от наличия сопутствующего заболевания: 1 группа – 87 больных гипертонической болезнью, сахарным диабетом 2 типа в сочетании с ожирением; 2 группа – 71 пациент с гипертонической болезнью и сахарным диабетом 2 типа; 3 группа – 65 больных гипертонической болезнью с ожирением; группа сравнения состояла из 74 пациентов с гипертонической болезнью без ожирения и без СД 2 типа.

Параметры левого желудочка (ЛЖ) оценивали с помощью эхокардиографии по стандартной методике Фейгенбаума. HbA1c определяли турбулентиметрическим методом, а уровень глюкозы в сыворотке крови – иммуноферментным.

Результаты. При сравнении пациентов из трех групп с больными, имевшими изолированный вариант ГБ, наиболее значимое влияние на развитие неблагоприятного типа ремоделирования ЛЖ со значениями χ² = 29,371 и коэффициента контингенции Пирсона (С) − 0,393 (р < 0,05) обнаружено при одновременном влиянии сахарного диабета 2 типа и ожирения. Наличие сопутствующего СД 2 типа без ожирения имело значительную умеренную связь с развитием неблагоприятной геометрии ЛЖ, χ² = 11,029 и С = 0,266 (p < 0,05), что указывает на гораздо меньшее влияние на процесс по сравнению с полиморбидным эффектом СД 2 типа и ожирения.

Сравнение пациентов с сочетанием ГБ и ожирения с теми, у кого была только ГБ, не показало значительного влияния сопутствующего ожирения на развитие неблагоприятных типов геометрии ЛЖ со значениями χ² и С 0,529 и 0,062 соответственно (p > 0,05).

Выводы. Гипертоническая болезнь при полиморбидности с сахарным диабетом 2 типа и ожирением, но не в сочетании только с сахарным диабетом 2 типа или только с ожирением имеет наиболее значимую связь с гипертрофическими типами ремоделирования левого желудочка. Одновременное наличие сахарного диабета 2 типа с ожирением у гипертонизированных больных приводит к развитию преимущественно концентрической гипертрофии левого желудочка.

In recent years, more and more attention is paid to the importance of heart remodeling in essential hypertension (EH) with concomitant pathology and complications [1–4].

Structural and functional changes of the myocardium, the geometry of the left ventricle (LV) and its remodeling significantly depend on the presence of risk factors that lead to the development of systolic and diastolic dysfunction [5].

The Framingham study proved that LV hypertrophy is an independent factor in cardiovascular morbidity and mortality and it plays an important role in myocardial dysfunction. Besides, the probability of developing cardiovascular pathology in obese people is 50 % higher than in people with normal body weight.

In most cases, the degree of dilatation of heart chambers prevails in the presence of obesity. The size of the left atrium (LA) in obese patients is greater in comparison with the group of people with normal weight. The mechanisms leading to an increase in the LA size are identical to those that cause LF hypertrophy: an increase in body mass index (BMI), hypertension, volume overload and diastolic filling disorders. Framingham Heart Study showed a higher risk of atrial fibrillation among obese patients, which was due to an increase in the size of the LA.

A great attention should be paid to the features of myocardial LV remodeling among the other pathological processes affecting the state of the cardiovascular system in hypertensive patients with concomitant type 2 diabetes mellitus (T2DM) and obesity.

There are limited data about the level of combined influence of T2DM with obesity on the LV hypertrophy in patients with EH, whereas there is evidence of such impact of diabetes or obesity alone.
groups were age- and sex-matched (more than half of the patients were women). The average duration of EH in the main group was about 10 years, and in the comparison group, the duration of EH was approximately the same as in the main group. BMI in groups of patients was about 33 kg/m²; body surface area and height of patients in all groups were statistically equal. All the patients of the main group were matched by functional classes (FC) of heart failure (HF).

Inclusion criteria into the study were the presence of EH, T2DM, obesity, which were confirmed by various methods of examination. The clinical diagnosis was based on the patient complaints, anamnesis and physical examination. The diagnosis was confirmed using laboratory and instrumental methods in accordance with the recommendations of the European Society of Cardiology (2018).

The instrumental methods used were transthoracic echocardiography according to the standard method of H. Feigenbaum on an ultrasound machine "Philips HD11XE" (USA) in accordance with the generally accepted Echo-pulse method with an ultrasound frequency of 7.5 MHz. In the M-mode, the following parameters of the LV were determined: end-diastolic dimension (EDD) (cm), end-systolic dimension (ESD) (cm), LV posterior wall thickness (LVPWT) (cm), interventricular septal thickness (IVST) (cm). End-diastolic volume (EDV) and end-systolic volume (ESV) (ml) of the LV were calculated based on Simpson’s method (1991), followed by LV ejection fraction (EF) (%) measurement. LV myocardial mass index (iLVM) was calculated using the Devereux formula: $1.04 \times [(IVST + LVPWT + EDD)^2 - EDD^2] - 13.6$. The calculation of the LV myocardial wall thickness index (iLWT) was performed according to the formula: $iLWT = \frac{(LVPWT + IVST)}{EDD}$.

Then, the LV myocardial mass index (iLVM) was calculated based on height of patients: $iLVM (g/m) = \frac{LVM}{P}$, where $P$ – the height of patients (m). In addition, the LA (cm) and aorta (cm) size was determined.

Depending on iLVM and relative wall thickness (RWT), 4 types of LV remodeling in were defined: normal geometry (without changes), concentric remodeling (normal iLVM and increased RWT), eccentric hypertrophy (increased iLVM and normal RWT), concentric hypertrophy (increased iLVM and increased RWT) [4]. Than 2 groups were also formed: the first one was the hypertrophic type – eccentric and concentric hypertrophy, indicating an unfavorable, and the second one was non-hypertrophic type with normal geometry and concentric remodeling that was regarded as favorable. Such a categorization was done in accordance with contemporary international data [6–8].

T2DM diagnosis was established according to the WHO and IDF criteria with measuring fasting plasma glucose $\geq 7.0$ mmol/l (126 mg/dl) and 2-h venous plasma glucose after a 75 g oral glucose load $\geq 11.1$ mmol/l (200 mg/dl). HbA1c $\geq 6.5 \%$. HbA1c was determined in blood serum by turbidimetric method using the Liquidirect kit (Human GmbH, Germany). Serum glucose levels were measured by enzyme-linked immunosorbent assay using DRG kits (USA).

The study was carried out in the Biochemical Department of the Central Research Laboratory of the Kharkiv National Medical University of the Ministry of Health of Ukraine on an enzyme-linked immunosorbent analyser “Labline-90” (Austria).

Obesity and its degree were diagnosed based on the WHO classification criteria. Body mass index was calculated by the formula BMI = (body weight, kg) / (height, m²).

The exclusion criteria were: valvular heart disease; symptomatic (secondary) hypertension; concomitant endocrine, autoimmune, severe renal, oncological pathology; chronic obstructive pulmonary disease; exacerbation of chronic inflammatory processes or the presence of acute inflammatory diseases; cerebrovascular disorders; acute left or right ventricular failure; concomitant mental illness, alcoholism, drug addiction.

Statistical data processing was performed using Med Calc Version 19.3.1. (trial version) and SOFA Statistics 1.5.3 for Windows (open source AGPL3 license). For statistical processing of the results, parametric methods were used (the mean value – M, standard deviation – SD or standard error of the mean value – m). The results were presented as $M \pm SD$, unless otherwise indicated. The quantitative Kolmogorov–Smirnov test was used to ascertain the normality of distribution hypothesis. Significance of differences between groups was determined using Student’s t-test and the value of significance – $P$. A relationship between qualitative (attributive) features was measured via a $2 \times 2$ analysis using the four-field contingency table, with the chi-square ($\chi^2$) and Pearson’s contingency coefficient calculation.

Results

The baseline clinical characteristics of the enrolled patients are presented in Table 1. The patients from all groups were sex-, age-, smoking status-matched. Group 1 and 2 patients were matched by the severity of T2DM and group 1 and 3 – of obesity.

The types of LV remodeling were estimated during the examination of obese and non-obese patients with EH in the presence or absence of T2DM (Table 2).

The vast majority of patients with concentric hypertrophy (70.12 %) were found in the 1st group (Table 2), fewer patients were with eccentric hypertrophy (14.94 %) and concentric remodeling (14.94 %) in equal proportions. Both concentric (36.92 %) and eccentric hypertrophy (13.85 %) were less frequent among obese hypertensive patients, while there were more individuals with concentric remodeling (40.00 %) and normal geometry (9.23 %). Eccentric type (16.90 %) was revealed less often in the patient group of EH and concomitant T2DM, concentric hypertrophy (54.93 %) was more often, concentric remodeling (23.94 %) and normal geometry occurred in only 4.23 % of patients. The LV geometry in the EH group was as follows: 41.89 % of patients with concentric and 2.70 % – with eccentric hypertrophy and 27.03 % – with concentric remodeling and 28.38 % had normal geometry.

It is considered that concentric and eccentric types of LV remodeling (hypertrophic types) are rated among more prognostically unfavorable variants of heart geometry. The influence of comorbidity and polymorbidity on the development of adverse morpho-functional changes of the heart in hypertensive patients was evaluated. The distribution of patients with relatively favorable and unfavorable LV geometry variants was calculated. Thus, the unfavorable...
Table 1. Baseline characteristics of the examined subjects

<table>
<thead>
<tr>
<th>Parameter, units</th>
<th>EH + T2DM + Obesity</th>
<th>EH + T2DM</th>
<th>EH + Obesity</th>
<th>EH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.11 ± 12.56</td>
<td>58.59 ± 11.82</td>
<td>59.11 ± 12.48</td>
<td>58.03 ± 13.21</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35.76 ± 4.12</td>
<td>27.76 ± 4.83</td>
<td>36.43 ± 5.27</td>
<td>24.96 ± 5.76</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>37 (43)</td>
<td>29 (41)</td>
<td>26 (40)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.12 ± 1.56</td>
<td>7.25 ± 1.31</td>
<td>5.32 ± 1.23</td>
<td>5.05 ± 1.78</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>153.83 ± 19.21</td>
<td>155.51 ± 18.37</td>
<td>152.76 ± 20.09</td>
<td>154.90 ± 19.15</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>94.89 ± 11.54</td>
<td>95.14 ± 10.03</td>
<td>94.35 ± 11.01</td>
<td>95.61 ± 10.17</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>17 (20)</td>
<td>15 (21)</td>
<td>13 (20)</td>
<td>16 (22)</td>
</tr>
</tbody>
</table>

EH: essential hypertension; T2DM: type 2 diabetes mellitus; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Distribution of patients in the groups (by the presence of comorbid or polymorbid pathology) depending on the type of heart remodeling

<table>
<thead>
<tr>
<th>Type of geometry</th>
<th>EH + T2DM + Obesity</th>
<th>EH + T2DM</th>
<th>EH + Obesity</th>
<th>EH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal heart geometry,</td>
<td>0 (0)</td>
<td>3 (4.23)</td>
<td>6 (9.23)</td>
<td>21 (28.38)</td>
</tr>
<tr>
<td>patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric remodeling,</td>
<td>13 (14.94)</td>
<td>17 (23.94)</td>
<td>26 (40.0)</td>
<td>20 (27.03)</td>
</tr>
<tr>
<td>patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric hypertrophy,</td>
<td>61 (70.12)</td>
<td>39 (54.93)</td>
<td>24 (36.92)</td>
<td>31 (41.89)</td>
</tr>
<tr>
<td>patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccentric hypertrophy,</td>
<td>13 (14.94)</td>
<td>12 (16.90)</td>
<td>9 (13.85)</td>
<td>2 (2.70)</td>
</tr>
<tr>
<td>patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EH: essential hypertension; T2DM: type 2 diabetes mellitus.

Table 3. The values of Pearson’s $\chi^2$ criteria and contingency coefficients in the analysis of comorbidity or polymorbidity influence on the unfavorable variants of LV geometry development

<table>
<thead>
<tr>
<th>Statistical criteria</th>
<th>Group 1 in relation to the comparison group</th>
<th>Group 2 in relation to the comparison group</th>
<th>Group 3 in relation to the comparison group</th>
<th>Group 1 compared to group 2</th>
<th>Group 1 compared to group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\chi^2$</td>
<td>29.371 ($P &lt; 0.05$)</td>
<td>11.029 ($P &lt; 0.05$)</td>
<td>0.529 ($P &gt; 0.05$)</td>
<td>4.139 ($P &lt; 0.05$)</td>
<td>20.988 ($P &lt; 0.01$)</td>
</tr>
<tr>
<td>Pearson’s coefficient</td>
<td>0.393</td>
<td>0.266</td>
<td>0.062</td>
<td>0.160</td>
<td>0.348</td>
</tr>
</tbody>
</table>

The results suggested a significant strong association between polymorbidity and the formation of such LV remodeling types as concentric and eccentric hypertrophy. The presence of concomitant T2DM without obesity had a significant moderate correlation with the development of unfavorable LV geometry, the value of $\chi^2$ and Pearson’s contingency coefficient were as follows: 11.029 and 0.062, respectively, indicating a much lesser impact on the process compared to the polymorbid effect of T2DM coexisting with obesity. Comparison of patients with the combination of EH and obesity to those who had only EH, did not show a significant effect of concomitant obesity on the unfavorable variants of LV geometry development with values of $\chi^2 = 20.988$ ($P < 0.001$) and Pearson’s contingency coefficient of 0.348 compared to the influence of comorbid obesity.

**Discussion**

It is known that long-term EH leads to the development of LV remodeling, which is characterized by changes in its geometric model. LV remodeling is considered as a compensatory response to increased LV load, which includes changes in volume and iLVM. Changes in the LV normal geometry worsen the disease prognosis provoking ischemic injuries [5].

Structural changes in the heart in obese patients can be divided into the following main components: LV hypertrophy, changes in the cardiac tissue structure, changes in the size of the right ventricle and LA [9]. Some researchers have found an independent association between obesity and LV hypertrophy [10]. Some scientists hold that an increase in LV mass indexing to body surface area accounted for the effects of obesity is not pathological. Previous studies have shown that obesity causes dilatation of the heart chambers [11].

It has been demonstrated that higher LV wall thickness >1 cm increases the risk of fatal complications. The risk of adverse coronary events is increased in the case of greater iLVM. In addition, the presence of LVH signs increases by a third 5-year mortality rates in men and by a quarter – in women. The relative risk of sudden cardiac death was found to be associated with an increase in iLVM detected by echocardiography. Meanwhile, normalization of blood pressure and reducing the degree of hypertrophy lower the risk of sudden cardiac death [12–14].

(hypertrophic) type (concentric plus eccentric hypertrophy) was the most common in the group with polymorbidity – 85.06 % of patients, and it was the lowest type in the group with only EH – 44.59 %, while in the concomitant obesity subgroup – 50.77 % and in the subgroup with combined EH and T2DM – 71.83 %.

The analysis of the certain comorbidity influences (T2DM, obesity or their coexistence) on the development of unfavorable types of LV remodeling using Pearson’s $\chi^2$ criteria and contingency coefficient to compare the patients from three groups with EH alone, revealed the most significant impact of the T2DM and obesity combination ($\chi^2 = 29.371$ and Pearson’s contingency coefficient – 0.393) (Table 3).
The LIFE study and its additional analysis demonstrated the results according to which the presence of LVH and left bundle branch block signs on ECG increases the risk of cardiovascular death by 1.6 times, sudden cardiac death — by 3.4 times and hospital admission rate for heart failure — by 1.7 times [15].

The data from the Jackson Heart Study (USA) suggest that cardiovascular complications were statistically more common in patients with inappropriate LVM (>45 g/m² in women and >49 g/m² in men) [16]. The PAMELA study indicates 4 and 5 times increased risk of cardiovascular events and death in the presence of LVH signs on ECG [17].

Our study was aimed at attempting to use an easy statistical method as table 2 × 2 with χ² and Pearson’s contingency coefficient to find out the combined influence of diabetes and obesity on the development of LV remodeling in hypertensive patients and correlation degree, but apart from that, the study examined the influence of T2DM or obesity alone.

The study of Tan Li et al. was similar to the present one in some aspects, but it was investigation of hypertension with diabetes mellitus alone, without obesity [18]. Herewith, the authors concluded that hypertensive patients with diabetes mellitus had increased risk for LVH and concentric hypertrophy in the total and female patients separately, but on the other hand, they did not find an association of EH and diabetes mellitus comorbidity with LVH and abnormal geometrical patterns in men. In our study, there were no differences in the development of LV remodeling between male and female populations.

The data from another study carried out by Kirstie A. de Jong et al. [19] showed that metabolically non-healthy obese, T2DM and obese patients with T2DM can develop LV hypertrophy regardless of EH. These findings are consistent with our, but that study was focused on patients without hypertension.

One of the main findings of the present study is that patients with polimorbidity should be strictly followed up, as it can prevent the process of LV remodeling and improve outcomes [20,21].

Our study found that there were the most overt structural and functional changes in the myocardium in the patient group of EH combined with T2DM and obesity. Decreased LV functional capacity is an important indicator of myocardial compensatory reserve depletion and significantly affects the severity of clinical manifestations in hypertensive patients with T2DM and obesity.

It should be noted that our study had some limitations being limited in sample size of enrolled patients and cross-sectional in character. T2DM patients had only mild and moderate course, we did not analyze those with severe course. Consequently, further investigation on this problem with larger sample size and longer follow-up period is needed to find out the influence of comorbidity on the development of LV remodeling.

Conclusions

1. Primarily, polimorbidity of essential hypertension with type 2 diabetes and obesity, but not in combination with type 2 diabetes or obesity alone, significantly influences the parameters of left ventricle geometry.

2. Thus, the results obtained in the work indicate that the coexistence of type 2 diabetes mellitus with obesity in hypertensive patients leads to the development of LV concentric hypertrophy predominantly, while the presence of type 2 diabetes mellitus alone in hypertensive patients results in this type of remodeling one fifth less often. Obesity in hypertension is one third less significant in formation of concentric hypertrophy compared to polymorbidity influence.

The perspective for further scientific research lie in the field of the study on pathogenetic features of stage I, II, III EH associated with concomitant diseases, especially T2DM and obesity.

Conflicts of interest: authors have no conflict of interest to declare.

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