SEX-SPECIFIC ASPECTS OF TYPE 2 DIABETES MELLITUS IN COMORBIDITY WITH HYPERTENSION

The purpose of this investigation is to study individual clinical and diagnostic characteristics in patients with type 2 diabetes mellitus with comorbid essential hypertension (DM + HD) with consideration for sex difference. Participants and methods. We examined 41 patients with comorbidity of type 2 diabetes and hypertension (21 men and 20 women) and 30 patients without diabetes, but having a history of hypertension (14 men and 16 women) and 20 healthy individuals. Results. Systolic and diastolic blood pressure (SBP, DBP) is significantly higher in patients with comorbidity of DM+HD compared with HD (in men, only DBP), while the heart rate did not change. The protein content in urine was below normal values that indicates an early stage of the pathological condition. Women showed a high level of creatinine compared to normal value in both groups, although this indicator is lower compared to men and is statistically significant in DM + HD. In both groups, there were high numbers of left atrium size, end diastolic size (EDS) compared to normal value, while sex differences were noted: EDS was higher in men. The increased size of left atrium directly correlated with the end-diastolic size (higher in men), the thickness of the interventricular septum (TIVS), and thickness of posterior wall (TPW) (with DM + HD, higher in men). In men with DM + HD, the E/A was lower and the thickness of the intima-media complex (IMC) of the right common carotid artery (CCA) was higher than in the HD group. There were no statistically significant differences in the state of right and left common carotid arteries. The ejection fraction was lower compared to normal values. Conclusion. In patients with diabetes mellitus + hypertension and hypertension, the semi-dimorphic differences of TIVS, TPW, E/A, IMC of right CCA can be used to predict the development of pathological process. A decrease in level of protein in urine indicates absence of proteinuria, glomerular filtration disorders, which is due to early stage of formation of DM + HD pathological state in this category of patients. Absence of changes in area is associated with a sufficient excretory function of kidneys.

Key words: type 2 diabetes mellitus, hypertension, clinical and diagnostic indicators, men, women.

Introduction

Nowadays 425 million people suffer from diabetes mellitus (DM) [1]. Diabetes mellitus is one of the most prevalent diseases that can affect individuals across all segments of the population. The number of people with diabetes aged 20-79 years was predicted to reach 642 million (uncertainty interval: 521-829 million) by 2040 [2]. On a global scale, diabetes hits particularly middle aged people between 40 and 59 years that causes serious economic and social burden. Furthermore, diabetes affects especially low and middle income countries, as 77 % of all people with diabetes worldwide live in those countries [3]. Diabetes mellitus is among ten leading causes of death in the world, killing about 1.6 million people a year, and is considered the third largest risk factor for premature death worldwide due to hyperglycemia, oxidative stress caused by hyperglycemia, and inflammation [4]. The main cause of death and disability among patients with diabetes is cardiovascular diseases (CVD) [2, 5]. Diabetes mellitus aggravates mechanisms underlying atherosclerosis and heart failure [5]. Multifactorial CVD risk reduction with lipid-lowering drugs, antihypertensive therapy, and hyperglycemia reduction contribute to decrease in incidence of cardiovascular complications, but their level remains higher for patients with diabetes than without it.

The prevalence of type 2 diabetes differs by gender, region and socio-economic level [6, 7]. The incidence of type 2 diabetes among men is increasing at faster rate; especially this trend is noted in the Middle East countries [7]. Type 2 diabetes is more commonly diagnosed in men, but the most prominent risk factor obesity is more common in women [2, 6]. As a rule, there are large differences in gender ratios between countries. Differences in biology, culture, lifestyle, environment, and socio-economic status influence differences between men and women in predisposition, development, and clinical presentation of diabetes. Genetic effects and epigenetic mechanisms, diet and sedentary behaviour affect risk and complications differently in both genders. In addition, sex hormones have a great impact on energy metabolism, composition, vascular function and inflammatory responses. Endocrine imbalance is associated with adverse cardiometabolic features seen in women with an excess of androgens or in men with hypogonadism. Psychological stress has a greater impact on women. In addition, women with diabetes have...
more cardiovascular disease (CVD), the risk of myocardial infarction and death from stroke than men and compared to non-diabetic subjects. Additional research on the semi-dimorphic pathophysiological mechanism of type 2 diabetes and its complications may contribute to more individualized diabetes management in future and raise awareness of gender-related risk factors.

Recent advances have sparked an explosion of “new” markers for the risk of diabetic kidney disease (DKD), but their clinical use remains limited [8]. Many clinical and biochemical characteristics are associated with progressive DKD. Among them - an increase in the concentration of glycated haemoglobin, systolic blood pressure, the degree of albuminuria, an early decrease in the glomerular filtration rate, the duration of diabetes, age, as well as the concentration of uric acid in blood serum, presence of concomitant microvascular complications, positive family history. With help of readily available clinical data, significant progress has been made in predicting the development of DKD, although it is believed that further work is required to consolidate data and facilitate clinical implementation of the results of new studies published area of DKD risk stratification. This work includes new markers requiring new and potentially expensive tests, so research on use of clinically available risk markers remains relevant.

Aim - to study individual clinical and diagnostic characteristics of type 2 diabetes to ensure predicting possibility of type 2 diabetes development in patients with CVD, in particular with hypertension (HD), taking into account sexual dimorphism.

Materials and methods

We examined 41 patients with type 2 diabetes in combination with hypertension (21 men and 20 women), as well as 30 people in comparison group - without diabetes with a history of hypertension (14 men and 16 women) and 20 healthy individuals (12 men and 8 women). The diagnosis of type 2 diabetes was established according to WHO criteria, according to level of glycosylated haemoglobin 6.5% (2011), stage of hypertension - according to WHO recommendations and International Hypertension Association (2007). All patients underwent a general clinical examination, which included collecting of complaints, anamnesis of illness and life, conventional physical research methods (examination, percussion and auscultation). Laboratory research included clinical blood and urine tests, daily urinary protein excretion; general biochemical - blood lipid spectrum, level of transaminases, glucose, urea and creatinine, blood uric acid concentration. Morphological changes in carotid vessels were assessed by quantitative echocardiography using an Ultima PA ultrasound scanner (Radmir, UA) with a linear probe with a frequency of 5-10 MHz.

Global left ventricular (LV) systolic function was assessed by ejection fraction (EF). The quantitative indicator of EF was calculated by the formula: EF = SV / EDV x 100, where SV is the stroke volume, EDV is the end-diastolic volume.

The examinations were carried out during hospitalization, while patients were under influence of regular antihypertensive therapy. Informed consent was obtained from all examined individuals to participate in the study and to use their bioassays.

Statistical processing was performed using Student’s t-test and Excel software.

Results

The control group is comparable in age and sex with the research groups. Analysis of the data of clinical diagnostic and functional indicators of the control group showed compliance with the normal numbers described in the literature.

Research groups consisted mainly of middle-aged and elderly people (Tables 1, 2). According to the International Diabetes Federation 2017, the global prevalence of diabetes among the age group 20–79 years is 8.8% [9].

Table 1. Clinical characteristics of patients considering the sex factor

<table>
<thead>
<tr>
<th>Indicators, normal</th>
<th>Control</th>
<th>DM 2d type, HDII, n=41</th>
<th>Comparison, HDII, n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>n=20</td>
<td>male n=20 female n=21</td>
<td>male n=14 female n=16</td>
</tr>
<tr>
<td>Age, years</td>
<td>43-55</td>
<td>40-78</td>
<td>48-79</td>
</tr>
<tr>
<td>SBP, 120-139 mmHg</td>
<td>122.3±12.5</td>
<td>190.5±5.8</td>
<td>187.0±3.5***</td>
</tr>
<tr>
<td>DBP, 80-89 mmHg</td>
<td>74.2±5.2</td>
<td>109.0±2.2***</td>
<td>108.0±2.0***</td>
</tr>
<tr>
<td>Heart rate, 60-90 beats per min</td>
<td>76.1±3.5</td>
<td>83.7±2.5</td>
<td>78.9±2.8</td>
</tr>
<tr>
<td>Daily protein, 0.08-0.10 g/l</td>
<td>0.010±0.003</td>
<td>0.020±0.008</td>
<td>0.030±0.007***</td>
</tr>
<tr>
<td>Creatinine, mmol/l</td>
<td>73.2±7.52</td>
<td>105.0±7.5</td>
<td>88.3±6.4***</td>
</tr>
<tr>
<td>Urea, 2.5-8.3 mmol/l</td>
<td>5.5±0.7</td>
<td>6.3±0.5</td>
<td></td>
</tr>
</tbody>
</table>
| Notes: * - the degree of differences probability with the comparison group <0.05, <0.01, <0.001; ♥♥ - with male <0.05, <0.001, respectively
We noted high levels of SBP and DBP compared to normal values both in the group of type 2 diabetes in combination with HD II (DM + HD) and in the comparison group (HD) (Table 1). At the same time, in DM + HD group, SBP and DBP are significantly higher than in the HD group (both indicators are reliable in women and only DBP in men). The absence of changes in heart rate and urea concentration was shown. Low levels of protein in daily urine were observed in both groups, reliably relative to the comparison group only in women with diabetes mellitus + hypertension. Women showed a high level of creatinine compared to normal value in both groups, although this indicator is lower compared to men, it is statistically significant in DM + HD.

In both groups, there were high numbers of left atrium size, end diastolic size (EDS) compared to normal value, while gender differences were noted: EDS was higher in men (Table 2). There were higher values of posterior wall thickness (TPW) in DM+HD compared with HD with gender differences in both groups, and in men with DM+HD, TPW was higher than normal values. The nature of changes in the rest of analyzed indicators was less pronounced. EF, thickness of the intima-media complex (IMC) of right common carotid artery (CCA) is below normal values in all examined patients, aortic diameter, ratio of early and late movement speed (E / A) are within the normal range in both men and women, and IMC of left CCA is below normal values only in men. CCA is the first functional and morphological level of blood vessels (large great vessels) in the algorithm of complex ultrasound examination of cerebral vascular system [10]. There were no statistically significant differences in the state of right and left common carotid arteries. In addition, men with DM + HD have lower E / A and higher IMC of right CCA compared with the HD group.

**Discussion**

An increase in SBP, DBP in all patients and a decrease of level of echocardiographic marker of cardiovascular risk E / A (in men with diabetes + HD) can be considered a reflection of concomitant hypertension; at the same time, an increase in systemic blood pressure is recognized as an important factor in progression of chronic kidney disease (CKD) [11]. And the absence of changes in E / A indicates normal nature of diastolic function of left ventricle. At the same time, heart rate is also within the normal range, rapid heartbeat is compensation for heart failure.

Changes in the levels of biochemical parameters reflecting functional state of kidneys, daily protein, creatinine, urea, allow them to be directly associated with the development of diabetic nephropathy (DN). The absence of increase in level of protein excreted in urine, and vice versa, its decrease indicates absence of proteinuria, glomerular filtration disorders, protein absorption in nephron tubules, which is due to the early stage of pathological condition formation. Some manifestations of renal dysfunction development are observed only in women with DM + HD. The absence of changes in urea is associated with a sufficient excretory function of kidneys. And only increase in creatinine concentration in serum of women compared to norm, especially with DM + HD, indicates a decrease in renal filtration level. Creatinine is not considered a sensitive indicator for mild to moderate kidney damage. In patients with advanced CKD, serum creatinine and glomerular filtration rates can vary widely [11]. The main value of serum creatinine determination is the diagnosis of renal failure.

An increase of left atrium (LA) size is associated with the development of adverse cardiovascular events. The LA performs three main physiological functions that affect LV filling and its function [12]. The LA functions, firstly, as a pump that provides 15-30% of LV filling, and secondly, as a reservoir for venous return from the lungs during ventricular systole and as a conduit, providing blood flow from the LA to LV in the early diastole phase. An increase in the LA size directly correlates with such parameters of heart structure as EDS (higher in men), TIVS (with DM + HD, higher in men), and TPW (with DM + HD, higher in men). In this case, EF tends to decrease.
The ability to recognize changes in these predictors in patients with diabetes mellitus + hypertension will make it possible to identify patients at high risk and reduce the rate of development of DN as a result of treatment [11].

A decrease in IMC in all examined patients indicates absence of increase in stiffness of carotid artery wall; absence of unstable atherosclerotic plaque formation [13]. IMC changes are absent, although the presence of hypertension in patients with type 2 diabetes is associated with impaired blood rheology and hemodynamics of the blood supply to the brain. With increased blood pressure, average, maximum, minimum and volumetric linear blood flow velocities are reduced [10]. This is associated with an increase in muscle tone of vascular wall and peripheral resistance, as well as with a decrease in CCA elasticity. In patients with diabetes mellitus + hypertension, increase in blood flow velocity in diastole and a decrease in pulsation index, cerebrovascular reactivity index are noted, which is associated with morphological changes in carotid artery wall and a decrease in adaptive and compensatory capabilities of cerebral arteries [13]. Carrying out regular antihypertensive therapy even at high normal blood pressure prevents development of hypertensive remodelling of carotid arteries, which contributes to prevention of cerebrovascular accident [10]. This can also explain absence of changes in aorta diameter in examined patients.

Importance of obtained results in aspect of molecular mechanisms of the development of type 2 diabetes studying should be noted [9]. Treatment of type 2 diabetes at an early stage, stage of pre-diabetes, helps to prevent further progression of diabetes, prevent development of microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (stroke, CVD and peripheral arterial disease) changes. Type 2 diabetes is characterized by a high incidence of vascular complications (diabetic retinopathy in 72.2 %; diabetic nephropathy in 68.7 %; micro-, macroangiopathy of lower extremities in 99.4 %; stroke - 7.1 %; myocardial infarction - 4.9 %, arterial hypertension in 54.9 %). Vascular complications (micro- and macroangiopathies) occur in all patients. Prevailing in elderly men (from 60 to 69 years and older - 14.2 %.). Metabolic disorders reflecting state of carbohydrate and lipid metabolism are more pronounced in men, as well as a severe form of the disease, but these differences do not differ significantly with age.

Men with type 2 diabetes are more likely to suffer from microvascular complications than women, but presence of diabetes leads to earlier death of women from diseases of the circulatory system: average life expectancy in myocardial infarction and cerebrovascular diseases is reduced by about 5 years. Between 2000 and 2019, the age-standardised diabetes mortality rate increased by 3%. In lower middle-income countries, the diabetes mortality rate increased by 13 %. [14]. In this aspect, it is also interesting to note that in men with hypertension and diabetes mellitus + hypertension, changes in calcium concentration are caused by Ca\(^{2+}\)-related age-related change. Vascular calcification contributes to the high risk of cardiovascular mortality in chronic kidney disease (CKD) patients. Dysregulation of calcium (Ca) and phosphate (P) metabolism is common in CKD patients, and drives vascular calcification. Elevated serum P is now recognized as a major risk factor for cardiovascular events in chronic kidney disease, as well as the general population. Mortality in end stage renal disease patients is strongly correlated with serum P levels greater than 5.5 mg/dL [16]. With diabetes + HD, the concentration of phosphorus is higher in women, more in middle age, which may lead to an increase in the risk of CVD. The lifetime risk of diabetes is greater in women than in men and women with diabetes have a greater prevalence of diabetic kidney disease (DKD) risk factors including hypertension, hyperglycemia, dyslipidemia, and obesity [15].

It should also be noted that kidney is under influence of sex hormones [17]. Estrogens are sub-class of female steroid hormones, produced mainly by ovarian follicular apparatus in women. Also they are produced by testis in men, adrenal cortex and other extragonadal tissues (including bone, brain, adipose tissue, skin, and hair follicles) in both sexes. After menopause, only a small amount of estrogen is formed in women body (with extinction of ovarian function, estrogens are formed in peripheral tissues from dehydroepiandrosterone, synthesized by adrenal glands). Estrogens play a beneficial role in progression of some chronic kidney disease. Estrogens act on cells of nephronic component, regulating several processes at this level. One of the most important actions of estrogens is protective effect on kidneys; estrogens weaken glomerulosclerosis and tubulointerstitial fibrosis. Thus, estrogens have a nephroprotective effect. Estrogens play an important role in disorders of calcium-phosphorus metabolism: they have a beneficial effect on renal osteodystrophy - the main consequence of calcium-phosphorus disorders. Hormonal dysfunction in chronic kidney disease is clinically associated with sexual dysfunction, which affects the quality of life of these patients.

**Conclusions**

1. At DM + HD group, compared with HD, SBP and DBP are significantly higher (in men, only DBP), and F / A does not change, which indicates the normal nature of diastolic function of left ventricle in this category of examined patients, heart rate is within normal limits.

2. A decrease in level of protein excreted in urine indicates absence of proteinuria, glomerular filtration disorders, which is due to early stage of formation of DM + HD pathological state in this category of patients. Absence of changes in urea is associated with a sufficient excretory function of kidneys.
3. An increase in the size of LA directly correlates with the EDS (higher in men), TIVS (with DM + HD, higher in men), and TPW (with DM + HD, higher in men). Men with DM + HD have lower E / A and higher IMC of right CCA compared with HD group. In this case, the EF decreases. There are no changes in aorta diameter, which may be due to prevention of development of carotid arteries hypertensive remodelling as a result of regular antihypertensive therapy in this category of patients.

4. At an early stage of formation of the pathological state of DM + HD, predicting possibility of type 2 diabetes development in patients with HD, taking into account sexual dimorphism, can provide an analysis of individual clinical and diagnostic characteristics of patients, in particular TIVS, TPW, as well as E / A, IMC right CCA.

Prospects for further research

In the future, we will investigate the specific characteristics of kidney function, cardiohemodynamic factors, and metabolic aspects related to cardiometabolic risk in patients with diabetic kidney disease during wartime. This condition is often induced by disturbances in purine and carbohydrate metabolism, and our research will consider the influence of the arginine-vasopressin system's activity and the polymorphic variants of the eNOS and AGTR1 genes.

References

14. WHO. DIABETES [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes