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EARLY RENAL DYSFUNCTION IN OBESE PATIENTS WITH INSULIN RESISTANCE

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Abstract

Background and aims. *Obese individuals have insulin resistance status assessed in the present study by the HOMA index ("Homeostasis model assessment"). This prospective study assessed renal disorders in the insulin resistance in obese patients.* ***Material and Methods.*** *The study included 73 young obese patients. The assessment included the HOMA index before meal and parameters of renal function (glomerular filtration rate, albuminuria, β_2-microglobulinuria).* ***Results.*** *In young obese, insulin-resistance patients, glomerular hyperfiltration and β_2-microglobulinuria are found in 77.0 and 93.4% of cases respectively. The albuminuria is noted in some cases, which reduces diagnostic value.* ***Conclusions.*** *In young obese patients with insulin resistance, glomerular hyperfiltration and β_2-microglobulinuria are main diagnostic markers of renal dysfunction.*

key words: *insulin resistance, obesity, HOMA-IR index, glomerular filtration rate, β_2-microglobulinuria.*

Background and aims

The phenomenon of the XXI century is a significant predominance of obesity in most countries. Obesity is an important risk factor for many serious medical problems that lead to a decrease in the quality of life, a significant increase in morbidity and premature death [1-3].

The American Association of Clinical Endocrinology and the American College of Endocrinology has proposed a new name for obesity in 2016, namely Adiposity-Based Chronic Disease. This name does not replace the term of “obesity”, but it helps the doctor, regardless of specialty, to focus more upon the physiopathological implications of overweight [1].

The interconnection of obesity with disorders of the carbohydrate metabolism, including type 2 diabetes, continues to be of great interest, primarily due to the need to develop effective approaches to preventing damage of the target organs such as the cardiovascular system and the kidneys. Since for today the presence of general mechanisms of formation of cardiovascular complications and nephropathy of metabolic disorders has been proved [9-11].

According to epidemiological studies, there is a direct relationship between excess body

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weight and chronic kidney disease (CKD) [10]. The literature clearly shows the role of obesity as a predictor of CKD, regardless of the presence of such classical risk factors as AH and DM type 2. In addition, published epidemiological studies proved the effect of obesity on renal dysfunction, regardless of these diseases [9-12].

Among the target organs, which are affected with abdominal obesity, the kidneys occupy a special place. It is proved that among the life-threatening complications of obesity first place is cardiovascular, but one of the clearest trends for today is the increase in the number of cases CKD in this category of patients. It should be emphasized that the kidneys are not only a passive target organ of obesity, but also an active participant in the processes of nonadaptive organ remodeling. In the development of renal damage, there is a further increase in the risk of cardiovascular complications, which, in turn, makes the problem of obesity affecting the CKD more relevant [11].

Currently, the presence of obesity in a person is most frequently evaluated by body mass index (BMI) [3]. Although several versions of obesity classification are accepted, the most commonly used is the one proposed by the World Health Organization (WHO) which evaluates the BMI, as follows; underweight: BMI <18.5 kg/m^2, low risk of comorbidities associated with obesity; normal weight: BMI = 18.5-24.9 kg/ m^2; overweight: BMI = 25-29.9 kg/m^2, mildly increased comorbidity risk associated with obesity; Obesity Class I: BMI = 30-34.9 kg/m^2, moderately increased comorbidity risk; Obesity Class II: BMI = 35-39.9 kg/m^2, increased comorbidity risk; Obesity Class III or morbid obesity: BMI> 40 kg/m^2, very high comorbidity risk. A BMI between 40 and 50 kg/m^2 defines morbid obesity and a BMI of over 50 kg/m^2-the super obese category of individuals [2].

HOMA index. The main method for assessing insulin resistance is called "euglycemic clamp" which establishes a certain amount of ingested glucose after which the basal level of blood sugar remains constant meanwhile the blood insulin maintains at a constantly increased level. Depending on the insulin sensitivity status, the amount of ingested glucose will show variations from one individual to another [4]. However, the method is accessible only in specialized centers, being laborious and time - consuming, therefore simpler alternative methods have been proposed over time, including the HOMA index [5]. Matthews et al. describe in 1985 the HOMA index ("Homeostasis model assessment") based on the assumption that insulin blood levels and blood sugar levels before meal with or without normal glucose tolerance are set at a specific level of their own organism.

HOMA-IR = (IB (μU / L) x GB (mmol / L)) / 22.5, where IB represents basal blood insulin levels before meal, and GB basal glycemia before meal. HOMA index reference values [6-8]: −< 2-normal; −2: possible resistance to insulin; − 2.5: increased probability of insulin resistance; −5: the mean value in diabetes.

Material and Methods

The clinical work was conducted at the Endocrinological Department of the Dnipropetrovsk Clinical Hospital № 9. 73 patients were examined of the study. To I (main) group included 61 patients of the young age (WHO, 1963), with abdominal adiposity of I-III degree, with or without hypertension, I-II stage, 1 degree, moderate or high risk. The control group included 12 young healthy people.

Criteria for inclusion in the study: alimentary-constitutional form of abdominal obesity (BMI greater than 30 kg/m^2) with or without hypertension, I-II stage, 1 degree, moderate or high risk; the lack of regular antihypertensive and / or body weight correction for 6 months before being included in the study.

Criteria for exclusion from the study: patient refusal; secondary forms of obesity; secondary arterial hypertension; chronic kidney disease and severe liver disease in history; the presence of organic pathology from the cardiovascular system; diabetes mellitus type 1; failure of any chronic diseases.

The research was conducted on the developed program with careful evaluation of anamnestic, general clinical and laboratory indices, results of instrumental research methods.

We analyzed the GFR for 24-hours daily urine test (Reberg-Tareyev test) with correction for body surface area [10]: Reberg-Tareyev test corrected for the surface area of the body: GFR (ml / min / 1.73m^2) = creatinine urine x minute diuresis x 1.73 / body surface area / blood creatinine. Investigation of the urine albumin excretion level was performed by the Bradford method on a Humareader ("Human", Germany) plate-length photometer with a wavelength of 630 nm. It is classic markers of glomerular dysfunction in patients with CKD. In healthy people level of albuminuria should not exceed 30 mg / 24 hours. The value of albuminuria < 10 mg / 24 hours is considered optimal, 10-30 mg / 24 hours – normal [11].

β_2-microglobulin in the urine was determined by immunoturbidimetric method on a flatbed photometer "Humareader" ("Human", Germany) at a wavelength of 630 nm. β_2-microglobulin is a low molecular weight protein that is well-filtered through the glomerular barrier and is normally completely reabsorbed and catabolized in the proximal tubules. Increased excretion of β_2-microglobulin (> 0.3 μg / ml) is a specific marker of proximal tubular dysfunction in individuals with CKD.

Statistical analysis

Statistical processing of research results was carried out by the methods of variation statistics implemented by the standard package of applications "STATISTICA® 6.1", serial number of the license AGAR 909E415822FA; Medcalc® Version 12.7.0.0.; Microsoft Excel. The Kolmogorov-Smirnov single-assembly test was used to test the hypothesis of normal distribution. When describing quantitative characteristics, the median (Me) and interquartile scale (25%, 75%), for qualitative signs - in relative values are determined. The significance level was considered to be significant at $p<0.05$.

Results and discussion

The median age of patients in the I group amounted to 36.0 (28.0; 42.0) years, among them men - 29 (47.5%), women - 32 (52.5%). Patients in group I were divided into 2 subgroups depending on the presence of hypertension: Ia (without AH) subgroup (n = 31) and Ib (with AH) – subgroup who has hypertension I-II stage, 1 degree, moderate or high risk (n = 30).

The control group included 12 people (median age - 29.0 (24.0; 33.5) years, among them men - 6 (50.0%), women - 6 (50.0%), median BMI - 22.3 (21.0; 23.0) kg / m^2.

Results of HOMA-IR are presented in Table 1 and showed that the maximum values are characterized by a main group of patients, with minimal values - control group. In analyzing the revealed violations, it should be noted that the indicators of all the examined obese patients, coincide with the indicators of the cohort, which is to be examined for asymptomatic undiagnosed type 2 diabetes.

The analysis of the indicators of renal function of the subjects (Table 2) showed that the maximum values of GFR are characterized by the main group of patients, the minimum values–control group. General characteristics of indicators of functional state of the kidneys of the patients in table 2-3. The study showed the presence of glomerular hyperfiltration in almost 47 (77.0%) people with abdominal obesity, regardless of the presence of hypertension. Normal values of GFR were observed in almost 14 (23.0%) persons the main group and all control group. It is proved that the investigated persons of the main group are significantly differ in the level of GFR in 1.6 times GFR of the control group (p<0.001).

Table 1. Results of HOMA-IR.

Parameter	I group, n=61	Control group, n=12
HOMA-IR	8,2 (6,0;12,1)*, p<0,001	1,7 (1,4;1,9)

Notes: p - the reliability of the differences with the control group

Table 2. Analysis of the indicators of renal function.

Parameter	I group, n=61	I a subgroup, n=31	I b subgroup, n=30	Control group, n=12
GFR, ml / min / 1.73m^2	158,8 (141,9; 188,0)*,p <0,001	163,0 (142,4; 186,7)*, p <0,001	152,6 (140,0; 215,0)*,p<0,001	101,3 (97,4; 105,5)
Albumin in daily urine, mg / 24 hours	7,0 (5,1;15,1)* p<0,01	6,7 (5,0;9,0)* p<0,05	7,7 (5,2;27,1)* p<0,01	4,1 (3,2;6,2)
β_2-microglobulin in urine, µg / ml	1,8 (0,8;3,6)* p<0,001	2,1 (0,9;3,6)* p<0,001	1,3 (0,6; 3,6)* p<0,001	0,2 (0,1;0,3)

Notes: p - the reliability of the differences with the control group

Analyzing the obtained data (Table 3), we can state the presence of UIA 7 (11.5%) patients in the main group. Normal values of albumin urine were found in all control and most patients in the main groups.

The study showed the presence of β_2-microglobulinuria in most patients in the main group. Normal values of this indicator were observed in the control group of patients and some obese patients.

Table 3. Presence of UIA.

Parameter	I group, n=61	I a subgroup, n=31	I b subgroup, n=30	Control group, n=12
Hyperfiltration, %	47 (77,0%)	24 (77,4%)	23 (76,7%)	–
Normal values of GFR, %	14 (23,0%)	7 (22,6%)	7 (23,3%)	12 (100%)
Albuminuria, %	7 (11,5%)	3 (9,7%)	4 (13,3%)	–
β_2-microglobulinuria, %	57 (93,4%)	30 (96,8%)	27 (90,0%)	–

Correlation analysis revealed a direct correlation between such parameters as the level of urine β_2-microglobulin and urine albumin excretion (r = + 0.55; p <0.001) in patients in the main group. It should be noted that there is a direct correlation between subjects such as GFR and the level of urine albumin excretion (r = + 0.48; p <0.001), irrespective of the presence hypertension; and β_2-microglobulin urine (r = + 0.57; p <0.001).

Thus, in group of persons with abdominal obesity the maximum values of HOMA-IR were stated. Statistical analysis of the indicators of renal function at the subjects showed that the maximum values of GFR and β_2-microglobulin in urine are characterized by the main group of patients, the minimum levels - control group. UIA were obtained in some obese people.

In patients with early signs of renal dysfunction, tubular and glomerular components of renal dysfunction are involved. With an increase in the level of GFR in patients with abdominal obesity, there is a presence of elevated levels of diagnostically significant proteins in the urine (UIA, β_2-microglobulinuria), which may be due to an increase in the permeability of the glomerular filtration of the nephrons. The revealed statistically significant direct proportional relationship between β_2-microglobulin and albumin levels makes it possible to use urine β_2-microglobulin as an early marker for subclinical kidney damage in individuals with abdominal obesity.

Conclusions

In young obese, insulin-resistance patients, glomerular hyperfiltration and β_2-microglobulinuria are diagnostic markers of renal dysfunction in 77.0 and 93.4% of cases respectively. The albuminuria in this category of patients is noted in some cases (11.5 % respectively), which reduces their diagnostic value in the early stages of kidney damage in young obese patients with insulin resistance. Determination of β_2-microglobulinuria in conjunction with albuminuria allow to evaluate not only the degree of violation of the selectivity of the glomerular filter, but also the severity of involvement in the pathological process tubular component.

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