

Original Research

Early metabolic disorders among medical students

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Received: 17 April 2020 / Accepted: 1 June 2020

Abstract

Background and aims: People suffering from cardiovascular diseases (CVD), chronic kidney diseases (CKD), and/or diabetes mellitus (DM) type 2 or at high risk of such diseases need early detection and management. The purpose is to investigate early metabolic disorders among medical students. **Materials and methods:** Investigated Group I – Ukrainian medical students (n=31) with abdominal obesity and control group (n=12, healthy students). **Methods:** Physical examination, medical history assessment, oral glucose tolerance test, HOMA-IR, blood lipids, urine albumin excretion (UAE), insulin, leptin, statistical methods. **Results:** Microalbuminuria is in 3 (9.7%) patients of Group I. From Group I, 5 (16.1%) were active smokers, 26 (83.9%) were never smokers. The mean smoking index in Group I was 5.0 (3.0; 7.0) packs/years, with correlation for UAE ($r=+0.39$; $p=0.02$). Hyperleptinemia was found in 30 (96.8%) patients in Group I ($p<0.01$), with correlation for UAE ($r=+0.75$; $p<0.001$). In Group I, 8 (25.8%) patients had IFG and 9 (29.1%) IGT; 27 (87.1%) – hyperinsulinemia and 96.8% had IR (with correlation for UAE – $r=+0.73$; $p<0.001$). Decreased HDL and elevated levels of TG were found in Group I ($p<0.01$). **Conclusions:** In medical students with abdominal obesity we found hyperleptinemia; dyslipidemia; pre-diabetic conditions and insulin resistance. Microalbuminuria was revealed only in 9.7% of patients and indicates the early stages of glomerular kidney damage and the presence of endothelial dysfunction. Correlation analysis confirmed the predictive role of metabolic disorders for increasing UAE. The relationship between insulin resistance and urine albumin ($r=+0.73$, $p<0,001$) indicates a predictive role in the development of renal dysfunction.

Keywords: medical students, obesity, insulin resistance, leptin resistance, microalbuminuria.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide. CVD is the major factor affecting the prognosis of patients with chronic kidney disease (CKD). Among these patients' morbidity and mortality rates are 10–20 times higher than in the general population. Endothelial dysfunction, an intermediate cardiovascular endpoint, plays a significant role in the development of atherosclerosis and vascular lesions, which were associated with CKD, in addition to traditional CVD risk factors (e.g., hypertension and diabetes mellitus (DM)). Microalbuminuria was shown to be an independent risk

factor for cardiovascular disease in non-diabetic and diabetic patients in numerous studies [1–3].

Metabolic syndrome is increasingly associated with abdominal obesity. There is the evolution of clinical diagnosis in various guidelines (there is no international consensus on the diagnosis and definition of metabolic syndrome) [4].

Most cardiovascular diseases and type 2 DM can be prevented by taking action against such risk factors like tobacco use, unhealthy diet and obesity, physical inactivity and harmful alcohol use [5].

Thus, people suffering from CVD, CKD, and/or DM type 2 or at high risk of such diseases need early detection and management [6].



The aim of our study is to investigate early metabolic disorders among young people presenting as medical students.

Materials and methods

In our study, we evaluated the markers of metabolic disorders in Ukrainian medical students from 1 to 6 courses of SE “Dnepropetrovsk medical academy of the Ministry of Health of Ukraine” (n=31) with abdominal obesity without hypertension compared with a control group of healthy Ukrainian students (n=12) [7].

Criteria for inclusion in the study: young age (for WHO classification); an alimentary-constitutional form of abdominal obesity (BMI more than 30 kg/m²); the absence of regular weight-adjusting therapy for 6 months before enrollment.

Exclusion criteria: patient refusal; secondary forms of obesity; chronic kidney disease and history of severe liver disease; the presence of organic pathology by the cardiovascular system; DM type 1 or 2; decompensating of any chronic diseases; fever; following protein diet; severe physical activity.

The eligible patients who fulfilled the following inclusion and exclusion criteria and gave written informed consent were enrolled in the study. After obtaining written informed consent from all eligible patients a detailed history from the patient was taken.

The studies were conducted according to the developed program with careful evaluation of anamnestic, general clinical, and laboratory parameters. An assessment was made from the history of life, the family history of CVD and DM 2. Certain complaints were collected that indicated the risk of the development of these pathologies. Anthropometry was performed. Body mass index was defined as the ratio of body weight (kg) divided by square height (m²). Waist circumference was measured in the middle of the distance between the edge of the lower rib and the sacrum of the ilium.

The general complex of clinical examination at patients included oral glucose tolerance test, blood lipid spectrum, levels of albumin in urine, insulin, and leptin resistance. Daily urine

albumin excretion (UAE) studies were performed using the Bradford method on a Hum reader photometer (Human, Germany) at a wavelength of 630 nm. By criteria KDIGO (2012) microalbuminuria is a classic marker of glomerular dysfunction in patients with CKD. In healthy humans, albuminuria should not exceed 30 mg/24 hours. Albumin values of 10 mg/24 hours are considered optimal, 10–30 mg/24 hours are norm albuminuria, 30–300 mg/24 hours are microalbuminuria.

The determination of cholesterol, triglycerides, high and low-density lipoproteins was performed by enzymatic colorimetric method on a Hum reader (Human) photometer at a wavelength of 630 nm.

Determination of fasting glycemia and an oral carbohydrate tolerance test were performed by a glucose oxidase method on a Hum reader (Human), Germany, at a wavelength of 630 nm. To assess the state of carbohydrate metabolism, an oral glucose tolerance test was performed after 12-hour fasting. Patients did not take thiazide diuretics, contraceptives, glucocorticoids, followed diets with normal carbohydrate content. Fasting glycemia was determined, then for 5 minutes, the patient took 75 g of glucose solution in 250–300 ml of water, re-determined glycemia for 2 hours. For assessment of carbohydrate metabolism disorders were used criteria of diagnostics pre-diabetics and DM type 2 of ADA (2020).

Immunoreactive insulin was determined by enzyme-linked immunosorbent assay (ELISA) on a Hum reader photometer (Human, Germany) at a wavelength of 630 nm. The level of IR was calculated by the formula:

$$\text{HOMA-IR} = \text{insulin } (\mu\text{U/ml}) \times \text{glucose (mmol/l)} / 22.5$$

Beyond the limit of IR, in accordance with the recommendations of E. Bonora et al. adopted HOMA-IR equal to 2.77, which corresponds to the lower level of the upper quintile of the distribution of HOMA-IR values in healthy individuals of the European race with normal body weight [8].

Blood leptin was determined by enzyme-linked immunosorbent assay (ELISA) on a Hum reader (Human, Germany) at a wavelength of 630 nm. The result was obtained in the following units – ng/ml. Increases in blood leptin were

considered values: in men – 6 ng/ml, in women – >12 ng/ml.

Statistics

Statistical analysis of research results was performed 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 $p < 0.05$. To assess the relationship between the indicators, a correlation analysis was performed with Spearman rank correlation coefficients (r).

Results

In our study 43 Ukrainian medical students were examined. Group I included 31 young patients with abdominal obesity of I–III degree without hypertension. The median age of patients in Group I was 23.0 (19.0; 25.0) years, among them men – 14 (45.2%), women – 17 (54.8%). Median BMI was 33.1 (31.0; 37.4) kg/m². The control group included 12 healthy students. Median age was 22.0 (20.0; 24.0) years, among them men – 6 (50.0%), women – 6 (50.0%), median BMI – 22.3 (21.0; 23.0) kg/m².

Analyzing the obtained data, we revealed the presence of microalbuminuria in 3 (9.7%) patients of Group I. Normal values of urine albumin were found in all control subjects and in the majority of patients in the main group (Table 1).

From Group I of medical students 5 (16.1%) were active smokers, 26 (83.9%) were never smokers. The mean smoking index in the main group was 5.0 (3.0; 7.0) packs/years. Correlation analysis showed a direct moderate dependence of UAE with pack /years index ($r = +0.39$; $p = 0.02$) in patients with abdominal obesity, which confirmed other investigations [9]. Hyperleptinemia with a mean leptin level of 53.1 (27.9; 93.5) ng/ml was found in almost all – 30 (96.8%) patients in Group I compared with the control group ($p < 0.01$). It should be noted that urine albumin levels in the main group were significantly directly correlated with blood leptin levels ($r = +0.75$; $p < 0.001$) (Figure 1).

Prolonged abdominal obesity leads to impaired carbohydrate metabolism. The parameters of carbohydrate status OGTT were studied in patients with abdominal obesity and given in Table 2. In Group I 25.8% patients were revealed impaired fasting glucose and 29.1% – impaired glucose tolerance according to ADA criteria; 87.1% had hyperinsulinemia and almost all patients had insulin resistance. When analyzing the detected disorders, it should be noted that the parameters of all examined patients of Group I, coincide with those of the cohort to be examined for asymptomatic undiagnosed type 2 DM [10, 11].

Predictors of the presence of UAE in the main group were determined after correlation models of relationships with the studied carbohydrate metabolism parameters are presented (Table 3). Correlation confirmed the relationship between insulin resistance and renal function marker – UAE in patients with abdominal obesity (Figure 2).

A decreased HDL and elevated levels of total cholesterol and triglycerides were found in patients of Group I ($p < 0.01$), indicating an imbalance between total cholesterol and anti-atherogenic HDL (Table 4). The correlation between

Table 1: Average levels of albuminuria among groups of patients.

Marker	Group I (n=31)	Control group (n=12)	p-Value
Albumin in urine, mg/24 hours	6.7 (5.0; 9.0)	4.1 (3.2; 6.2)	$p < 0.05$

UAE and lipid metabolism in patients with abdominal obesity is given in Table 5.

Discussion

Microalbuminuria is an additional indicator of metabolic syndrome and a strong and independent marker of increased cardiovascular risk among individuals with and without DM. Therefore, microalbuminuria can be used for the stratification of risk for cardiovascular disease. Once microalbuminuria is present, cardiovascular risk factor reduction should be more “aggressive” [12]. Early signs of endothelial dysfunction manifesting with microalbuminuria have been found to be strongly correlated with central obesity, especially with the waist/hip ratio, and scientists report that abdominal obesity affects the

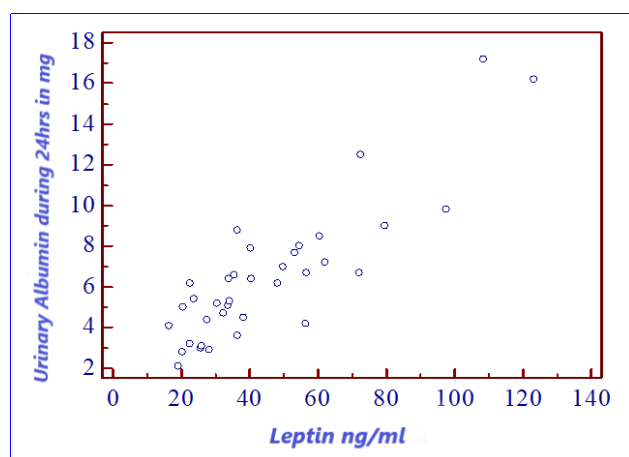


Figure 1: Correlation between urine albumin and blood leptin levels in subjects with abdominal obesity.

development of increased UAE in both men and women. In women suggest that waist measurement may improve identification of individuals without DM type 2 but with a high risk of microalbuminuria. Microalbuminuria is considered to be the first sign of kidney damage in abdominal obesity, their prevalence increases with increasing numbers of metabolic syndrome components [13, 14]. Particular importance in the damage of the target organs in obesity is related to leptin – the hormone involved in the formation of a sense of satiety. It is proved that patients with obesity develop resistance to leptin, and this is accompanied by its hyper-production. In leptin resistance, peroxidation of free fatty acids is activated, which can stimulate the development of lipotoxic changes, insulin resistance, endothelial dysfunction, oxidative stress. Leptin affects the calcification of blood vessels, the accumulation of cholesterol by cells of the vascular wall; increase the activity of the sympathetic nervous system in the presence of abdominal obesity and leptin resistance. In hyperleptinemia, local renal expression of transforming growth factor-beta (TGF- β) and its receptors are activated on the membranes of mesangiocytes and endothelial cells [15–17]. In studies Wolf, G. et al., have shown that hyperleptinemia, which is characteristic of obesity, initiates the development of glomerulosclerosis and proteinuria [18].

It is known that IR is a violation of the mechanisms at biological action of insulin, which is accompanied by a decrease in insulin-dependent glucose utilization by peripheral tissues.

Table 2: Characteristics the main markers of carbohydrate metabolism among students, abs /%, Me (25%; 75%).

Marker	Main group (n=31)	Control group (n=12)	p-Value
Glucose fasting, mmol/l	5.3 (4.6; 6.2)	4.0 (3.5; 4.5)	p<0.05
Patients with impaired fasting glucose, %	8 (25.8%)	–	–
Glucose after 2 hours loading, mmol/l	7.1 (5.7; 8.0)	5.6 (5.3; 6.1)	p<0.05
Patients with impaired glucose tolerance, %	9 (29.1%)	–	–
Insulin fasting, μ Un/ml	32.6 (28.2; 45.3)	13.0 (11.4; 15.8)	p<0.05
Patients with hyperinsulinemia, %	27 (87.1%)	–	–
HOMA-IR	8.2 (6.0; 12.1)	2.2 (2.1; 2.4)	p<0.05
Patients with insulin resistance, %	30 (96.8%)	–	–

The most characteristic sign of IR is hyperglycemia with absolute or relative hyperinsulinemia. But in some situations, the increase in insulin levels normalizes blood glucose due to persistent hyperinsulinemia, which promotes the development of atherogenic, hypertensive, and diabetogenic processes. Genetic factors (insulin receptor defect or post-receptor defect) contribute to the development of IR, as well as the influence of external factors, which include, first of all, the presence of obesity (especially abdominal) and the decrease in the volume of blood flow in the skeletal muscle capillaries. In turn, these disorders may be due to hypodynamic, hyper caloric

diets, and frequent psycho-emotional stress: those that are combined in the literature under the term “Western lifestyle” [19, 20].

Our data was proved by researchers, who found a significant association between UAE and insulin resistance or elevated blood glucose levels and demonstrated the central role of insulin resistance in the development of the metabolic syndrome and in increased cardiovascular risk in individuals with albuminuria. The researchers attributed the increased glomerular hemodynamic pressure and endothelial dysfunction to mechanisms that possibly link hyperinsulinemia and massive albuminuria. And have shown that hyperinsulinemia and insulin resistance are mediators of renal injury in obesity [21].

Lipid toxicity associated with obesity and metabolic syndrome may also contribute to the dysfunction of various organs, including the kidneys, mainly due to cellular accumulation of saturated fatty acids and TG. Hypoadiponectinemia, leptin resistance and impaired cytokine metabolism contribute to the intracellular accumulation of saturated fatty acids. Increased concentration of saturated fatty acids and their metabolites (acetyl-CoA, diacylglycerol, ceramide) affect the development of insulin resistance, have cytotoxic properties for β -cells of the pancreas, liver, heart, and endothelial cells, and also stimulate the synthesis. According to research, lipid toxicity in the

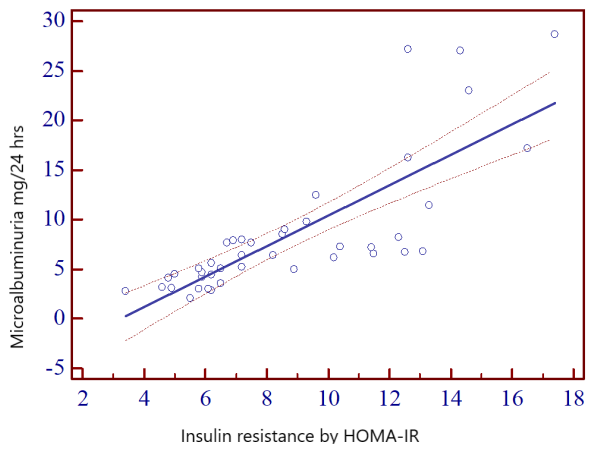


Figure 2: Correlation between insulin resistance and UAE at students with abdominal obesity.

Table 3: Correlations between carbohydrate metabolism markers and kidney functional status in individuals with abdominal obesity.

Marker	Glucose fasting	Glucose after 2 hours	Insulin	HOMA-IR
Urine albumin, mg/24 hours	r=+0.59 p<0.001	r=+0.53 p<0.001	r=+0.72 p<0.001	r=+0.73 p<0.001

Table 4: Profile of lipid metabolism in the groups, abs /%, Me (25%; 75%).

Marker	Main group (n=31)	Control group (n=12)	p-Value
Total cholesterol, mmol/l	5.4 (4.5; 6.3)	4.0 (3.4; 4.2)	p<0.01
Persons with high total cholesterol, %	17 (54.8%)	–	–
Triglycerides, mmol/l	1.3 (0.8; 1.9)	1,0 (0.7; 1.2)	p<0.01
Patients with high TG, %	11 (35.4%)	–	–
HDL, mmol/l	1.1 (1.0; 1.3)	1.3 (1.2; 1.4)	p<0.01
Persons with low HDL,%	20 (65.2%)	–	–

Table 5: Correlation between lipids and UAE in people with abdominal obesity.

Lipid marker	Correlation	p-Value
Total cholesterol, mmol/l	r=+0.51	p<0.001
Triglycerides, mmol/l	r=+0.62	p<0.001
HDL, mmol/l	r= -0.41	p<0.01

epithelial cells of the proximal tubules, whose clinical manifestation is proteinuria, leads to the development of tubulointerstitial inflammation, fibrosis, promotes the development of glomerulosclerosis and the progression of renal failure [22].

All medical students with abdominal obesity were recommended diet and exercise. Sweet drinks, beer, and alcohol were strictly forbidden [23].

Conclusions

1. In the examined medical students with abdominal obesity were found hyperleptinemia; dyslipidemia; disorders of carbohydrate metabolism in the form of pre-diabetes (impaired fasting glucose and impaired glucose tolerance), hyperinsulinemia and increased insulin resistance index HOMA-IR>2.77.
2. Despite the detection of microalbuminuria was only 9.7% of medical students with abdominal obesity, this marker already indicates the early stages of glomerular kidney damage in patients with abdominal obesity and the presence of endothelial dysfunction in young patients.
3. The correlation analysis established the predictive role of insulin resistance, hyperleptinemia, smoking, dyslipidemia, pre-diabetes in increasing albuminuria in persons with abdominal obesity.
4. A positive reliable relationship between insulin resistance and urine albumin ($r=+0.73$, $p<0.001$) indicates a predictive role for metabolic disorders in the development of renal dysfunction. It determines the importance

of identifying and managing young patients with abdominal obesity and high risk of cardiovascular and renal complications.

Acknowledgments of financial and material support

None.

Conflict of interest

The authors declare no conflict of interest.

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