MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp
EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 4 No. 11 (Nov - 2024) EJMMP ISSN: 2795-921X

EARLY DETECTION OF GLOMERULAR FILTRATION RATE ABNORMALITIES IN PATIENTS WITH INSULIN RESISTANCE BASED ON THE DEGREE OF OBESITY

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Abstract: This study investigated the relationship between obesity and glomerular filtration rate (GFR) in patients with insulin resistance. A significant knowledge gap exists regarding the early detection of kidney dysfunction in this population, highlighting the need for improved risk stratification and management protocols. The study included 100 patients with overweight and obesity (aged 25-44 years) who were divided into groups based on body mass index (BMI). GFR was calculated using the Cockcroft-Gault and MDRD formulas.The study found that patients with obesity had a significantly higher GFR compared to the control group, with a direct correlation between BMI and GFR calculated using the Cockcroft-Gault formula. Furthermore, the prevalence of GFR reduction (<60 ml/min/1.73 m²) was significantly higher in patients with obesity compared to the control group and general population. The findings suggest that patients with obesity are at increased risk for early-stage kidney damage, even with a high GFR, highlighting the importance of early detection and intervention.Chronic heart failure (CHF) remains one of the most pressing medical and socio-economic problems despite significant progress in treatment, as the prognosis for these patients remains unfavorable. Intensive study of the relationship between cardiovascular and kidney pathologies has led to the development of the cardiorenal syndrome concept.

Keywords: CHF, CKD, CVD, GFR. obesity, insulin resistance, glomerular filtration rate, early detection, risk factors, body mass index, hyperfiltration, adipokines, metabolic syndrome, lipotoxicity.

Relevance of the Study. According to WHO estimates, in 2016, more than 1.9 billion adults over 18 were overweight, with over 650 million suffering from obesity (WHO 2021). Therefore, obesity can be considered a new non-communicable "epidemic" of our time.Adipokines are hormones produced by adipose tissue, a subtype of cytokines secreted by adipocytes. Adipokines include: IL-6 (interleukin-6), TNFα (tumor necrosis factor), and leptin. It has been established that abdominal obesity and increased fat mass lead to an increased demand for insulin, contributing to the development of hyperinsulinemia and other signs of metabolic syndrome. Android obesity is associated with increased plasma levels of fatty acids, further enhancing the synthesis of very low-density lipoproteins and decreasing insulin sensitivity in peripheral tissues. The development of insulin resistance leads to decreased glucose uptake and increased blood glucose levels, which stimulates the pancreatic islets of Langerhans.Insulin resistance is a key pathogenetic factor in metabolic syndrome, representing a complex of compensatory-adaptive responses developing against a background of excess body weight. It also has an endocrine aspect as an early

reversible stage of type 2 diabetes mellitus. The development of insulin resistance leads to several negative pathophysiological systemic reactions capable of initiating destabilization mechanisms in cells and tissues of internal organs, including the kidneys, causing anatomical and functional disturbances.Treatment of chronic kidney disease (CKD) associated with obesity is still in its infancy, and scientifically based recommendations have yet to be developed. To improve the treatment of CKD associated with obesity, urgent improvements in risk stratification and management protocols are necessary. Although diabetes and hypertension significantly contribute to the development of CKD associated with obesity, studies in recent decades have shown that adipocytes are powerful endocrine cells that release adipokines that have a direct pathological effect on the kidneys. Adipokines also indirectly damage the kidneys by promoting insulin resistance and hypertension.Chronic low-grade inflammation is a biological hallmark of aging and is referred to as "inflammaging." Obesity promotes inflammation, explaining why people with obesity develop age-related chronic diseases prematurely. Conversely, limiting fat formation or stimulating the depletion of adipose tissue extends health and longevity. Both obesity and aging disrupt adipogenesis—the process by which adipocyte precursors differentiate into functional, insulin-sensitive adipocytes. Consequently, adipose tissue cannot buffer circulating lipids, which are then ectopically deposited in other organs such as the liver, skeletal muscles, and kidneys, causing lipotoxicity. Lipotoxicity disrupts insulin signaling in the kidneys, liver, and skeletal muscles, leading to insulin resistance.Individual adipocytes hypertrophy in response to impaired adipogenesis. Hypertrophic adipocytes contribute to adipose tissue inflammation by producing TNF-α and IL-6. These pro-inflammatory cytokines are critical for the development of insulin resistance; mice lacking TNF-α have lower levels of circulating free fatty acids and are protected from insulin resistance.Insulin resistance is considered the most pronounced manifestation of carbohydrate metabolism disorders and typically develops at early stages of type 2 diabetes. It serves as a special risk factor for the development of cardiovascular diseases and is an important therapeutic aspect of their treatment. Insulin resistance in kidney diseases develops as a result of metabolic syndrome. Blood insulin levels can mistakenly indicate the degree of insulin resistance, as kidney and liver function disorders affect insulin metabolism. Insulin resistance is an important therapeutic target in CKD. The kidneys are the immediate target of the damaging effects of all components of the so-called "deadly quartet," including insulin resistance. Damage also frequently affects cardiomyocytes, thus we should also speak of cardiorenal syndrome.Adiponectin secretion decreases with obesity, contributing to the development of chronic complications associated with obesity. The development of adiponectin knockout animal models has established causal links between adiponectin deficiency and certain aspects of metabolic syndrome. Serum adiponectin levels are lower in obese patients compared to lean individuals.Despite numerous renoprotective effects of adiponectin, its levels paradoxically increase in CKD and correlate positively with albuminuria, stage of CKD, and mortality, regardless of body mass index (BMI). Adiponectin also predicts adverse cardiovascular outcomes in patients with CKD. Unlike leptin, higher levels of adiponectin in CKD cannot be simply explained by reduced renal clearance since the liver clears high molecular weight forms of adiponectin. Thus, the question of why adiponectin levels are elevated in CKD and serve as a predictor of disease severity remains open.Numerous studies have demonstrated the existence of a fat-kidney axis, wherein cytokines and adipokines produced during obesity damage the kidneys, and metabolic dysregulation associated with CKD accelerates aging and dysfunction of adipose tissue. This axis is influenced by senescent cells and the presence of sleep apnea, which can enhance inflammation in obesity and CKD. Dysbiosis of the gut microbiome is another pathway that should be considered in obesity and CKD.Chronic kidney disease (CKD) causes significant morbidity, mortality, and healthcare costs worldwide. Obesity is a significant risk factor for the development of CKD, partly due to the high prevalence of diabetes and hypertension in obese patients. However, adipocytes also possess powerful endocrine functions, secreting numerous cytokines and adipokines that promote insulin resistance and cause chronic low-grade inflammatory states, thereby damaging the kidneys. The development of CKD is itself associated with various metabolic changes that exacerbate adipose tissue dysfunction and insulin resistance.

This fat-kidney axis is at the forefront of current research, considering the rising prevalence of CKD and obesity. Cellular senescence is a biological hallmark of aging, and age is another significant risk factor for obesity and CKD. Increased levels of senescent cells in adipose tissue predict renal dysfunction in animal models, and senotherapy may alleviate these phenotypes. In this review, we discuss the direct mechanisms through which adipose tissue contributes to the development of CKD, highlighting the potential clinical importance of such pathways in improving CKD treatment.Recently, the possibility of using one of the kidney biomarkers—cystatin C—to assess cardiovascular outcomes in CKD has been explored. Cystatin C belongs to the family of cysteine proteinase inhibitors, is expressed at a constant concentration in all nucleated cells of the body, and participates in extracellular and intracellular proteolysis, preventing its excessive activation by proteases. Its level does not depend on sex, age, or muscle mass and is regarded as a marker of kidney dysfunction that appears earlier than creatinine levels.Current studies have shown that cystatin C levels correlate with elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) ($r=0.57$; $p<0.0001$), left ventricular diastolic dysfunction ($r=0.34$; $p<0.001$), and right ventricular systolic dysfunction ($r=0.30$; $p<0.001$), and is considered a biomarker of increased risk of cardiovascular diseases regardless of the presence of CKD. However, there is very little data in the current literature regarding the potential use of cystatin C as a marker of myocardial injury in patients with CKD.

Research Objective: To assess kidney function based on glomerular filtration rate in relation to varying degrees of obesity.

Material and Methods. The study included 100 patients with overweight and obesity aged 25 to 44 years. Among them were 68 men and 32 women. The average age of the examined patients was 52.3 ± 5.2 years.All patients were examined at the Samarkand Regional Center for Nephrology and Dialysis. Patients were divided into groups according to BMI: Group 1 (control)—patients with normal BMI (n = 20), Group 2—overweight patients (n = 40), Group 3—obese patients (n = 40).

Exclusion criteria included acute myocardial infarction (within the last 3 months), acute cerebrovascular accidents, CHF III-IV degrees according to NYHA classification, liver disease in the decompensation stage, and oncological diseases.Obesity was diagnosed using bioimpedance analysis. The degree of obesity was determined based on WHO criteria from 1997 according to BMI. Instrumental studies included ultrasound examination (US) of the abdominal organs and kidneys. Laboratory tests included: complete blood count, urinalysis, biochemical blood analysis (Cystatin C, C-peptide, glycated hemoglobin, CRP, uric acid). Kidney function was assessed based on GFR, calculated using the Cockcroft–Gault formula (ml/min). CKD stages were determined according to the National Kidney Foundation's KDOQI guidelines.Data systematization and statistical processing were performed using the Statistica 6.0 statistical package. Methods used included descriptive statistics, comparison of means using Student's t-test, and assessment of significance (p).

Table 1: Characteristics of Observation Groups

Observation Group	Age	BMI (kg/m²)	Waist Circumference (cm)
Main Group	36.5 ± 6.3	33.2 ± 4.3	93.1 ± 10.3
Comparative Group	33.7 ± 6.4	37.1 ± 4.6	106.8 ± 13.5
Control Group	35.6 ± 5.9	21.4 ± 4.5	87.2 ± 14.9

"Upon analyzing the average GFR calculated using the Cockcroft-Gault formula, an increased GFR was found in all observation groups (Table 2)."Table 2: GFR According to Cockcroft-Gault Formula

Observation Group	GFR (ml/min)
Main Group	83.6 ± 1.4
Comparative Group	89.4 ± 1.1
Control Group	76.1 ± 1.4

It was noted that the average GFR increases with BMI: in cases of overweight, the average GFR was 93 ml/min, in obesity class I – 103 ml/min, class II – 109 ml/min, and class III – 129 ml/min. Statistical analysis revealed a high level of significance ($p < 0.001$).In the control group, the average GFR was 83 ml/min. Based on the calculations of GFR using the Cockcroft-Gault formula, it can be stated that patients with obesity have a high GFR, with a direct correlation: GFR increases with BMI, and the correlation coefficient is 0.35 ($p < 0.001$).When comparing the distribution results by stages of chronic kidney disease (CKD) with GFR calculated using the Cockcroft-Gault formula (ml/min) across different observation groups, a predominance of patients with high GFR was characteristic. The number of such patients increases with BMI: in the overweight group – 52%, in obesity class I – 69.8%, class II – 70.5%, class III – 90.9% had hyperfiltration. In the control group, accelerated filtration was determined in only 24.9%.Therefore, when distributing by stages of CKD according to GFR calculated using the Cockcroft-Gault formula, an inverse correlation was found between BMI and the stage of CKD: the higher the BMI, the lower the CKD stage, with a correlation coefficient of 0.26 ($p < 0.001$).According to the results of GFR calculations using the MDRD formula (ml/min/1.73 m²), the number of patients in stage III CKD with moderate reduction in GFR increases from 12% in overweight to 27.4% in obesity class II and to 23.4% in obesity class III (on average, every fifth patient).A group of patients with stage IV CKD was identified – 2.1% of patients with obesity class III.Thus, GFR calculation using the MDRD formula (ml/min/1.73 m²) allowed for the identification of a group of patients with severe and moderate reduction in GFR. On average, every fifth patient with obesity has moderate reduction in GFR, while in obesity class III, it is every fourth patient ($p < 0.001$). A significant correlation was found between BMI and GFR: the higher the BMI, the higher the CKD stage, with a correlation coefficient of 0.15, $p < 0.001$.Obesity is an important risk factor for the development of proteinuria and the terminal stage of kidney disease in the general population. This was confirmed in previous epidemiological studies – Current Opinion in Nephrology & Hypertension [2] showed that the likelihood of reduced GFR increases 1.3 times with a 10% increase in BMI [3–4].According to our data, on average, 23% of patients with obesity have moderate GFR reduction < 60 (ml/min/1.73 m²), which is 4.8 times, and in morbid obesity, 5 times higher than the number of patients in the control group and 1.8 times higher than in the general population.An inverse correlation was found between BMI and GFR: the higher the BMI, the lower the GFR, with a correlation coefficient of 0.15, $p < 0.05$.According to our research data, kidney damage occurs simultaneously with the development of obesity: stage I CKD is present in 15.4% of patients with obesity, stage II – 61%, stage III – 30.5%, stage IV – 0.9% (in morbid obesity – 2.1%). In the control group – 26.0%, 69.4%, 4.7%, and 0% respectively. Therefore, the prevalence of GFR reduction (< 60 ml/min/1.73 m²) in obesity exceeds the indicators of the control group by 6.5 times and the general population indicators by 6.8 times.The prevalence of severe kidney damage corresponding to stage IV CKD (GFR < 30 ml/min/1.73 m²) in patients with obesity is 4.5 times higher than in the population (in the control group, no patients with stage IV CKD were identified).The average GFR calculated using the Cockroft-Gault formula increases with BMI (105.1, 110.8, 135.6 ml/min for classes I, II, and III of obesity, respectively). In the control group, GFR is 82.5 ml/min. A direct correlation was found between BMI and GFR calculated using the Cockcroft-Gault formula, $r = 0.35$, $p < 0.001$.

Conclusion: The study revealed a significant association between obesity and early kidney dysfunction, even in individuals with high GFR. Patients with obesity demonstrated significantly higher GFR values compared to the control group, with a direct correlation between BMI and GFR calculated using the Cockcroft-Gault formula. However, the prevalence of GFR reduction (<60 ml/min/1.73 m²) was significantly higher in the obese group, highlighting the importance of early detection and intervention. These findings emphasize the need for comprehensive GFR monitoring in patients with obesity and insulin resistance, even in the absence of overt kidney disease. Early intervention strategies targeting weight management and addressing metabolic dysregulation could potentially mitigate the progression of kidney damage and improve long-term outcomes. Future research should investigate the impact of early intervention on GFR and kidney function in this high-risk population, exploring the potential benefits of lifestyle modifications, pharmacotherapy, and other interventions aimed at addressing the underlying mechanisms of obesity-associated kidney dysfunction. For patients with obesity, the GFR calculated using the Cockcroft-Gault formula is characterized by a high GFR. A direct correlation was identified between BMI and GFR calculated using the Cockcroft-Gault formula, with a correlation coefficient of 0.35, $p < 0.05$.

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