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IDENTIFICATION OF EARLY DISORDERS OF GLOMERULAR FILTRATION RATE DEPENDING ON THE DEGREE OF OBESITY

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Abstract:

Obesity contributes to the increased risk of several diseases including cardiovascular diseases, chronic kidney diseases, diabetes, hypertension, metabolic syndrome. Obesity is well known as an independent risk factor for chronic kidney disease. Glomerular filtration rate (GFR) is the best routinely available estimate for kidney function and essential for detection and management of both acute kidney injury (AKI) and chronic kidney disease (CKD). Creatinine is the most frequently used biomarker for eGFR. Creatinine may vary with factors not related to kidney function such as gender, muscle mass, ethnicity, and dietary factors. Cystatin C is an alternative biomarker for GFR-estimation which does not depend on muscle mass and thus fairly constant with age and gender.

Keywords: Chronic kidney diseases(CKD),glomerular filtration rate (GFR),adiponectin, obesity, body mass index, cystatin-C, insulin resistance, type 2 diabetes mellitus

Obesity is a chronic recurrent heterogeneous disease that develops under the influence of genetic, physiological and factors external environment and is characterized by excessive accumulation of adipose tissue, the dysfunction of which leads to numerous negative consequences[2, 7]. According to WHO, in 2016 about 2 billion people in the world are overweight and about 650 million of them are obese [5]. Obesity is one of the significant risk factors for many noncommunicable diseases, including hypertension, dyslipidemia, and some types of cancer[1]. Obesity is a triggering factor for diabetes associated with insulin resistance (IR). [39].Insulin is a hormone secreted by β cells of islets of Langerhans, controls the metabolism of carbohydrates, proteins, and fats by stimulating the absorption of molecules like glucose from the blood into fat, skeletal muscle cell, and liver [4]. Insulin resistance is identified as an impaired biologic response to insulin stimulation of target tissues, primarily the liver, muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. [7,10,13].
Progression of insulin resistance can lead to metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus [1].Insulin resistance is primarily an acquired condition related to excess body fat, though genetic causes are identified as well [9].
The gold standard for measurement of insulin resistance is the hyperinsulinemic-euglycemic glucose clamp technique. This is a research technique with limited clinical applicability; however, there are a number of clinically useful surrogate measures of insulin resistance, including HOMA-IR, HOMA2, QUICKI, serum triglyceride, and triglyceride/HDL ratio. In addition, several measures assess insulin resistance based on serum glucose and/or insulin response to a glucose challenge [8].

Adiponectin (a protein consisting of 244 amino acids and characterized by a molecular weight of 28 kDa) is a cytokine that is secreted from adipose tissues (adipokine). Available evidence suggests that adiponectin is involved in a variety of physiological functions, molecular and cellular events, including lipid metabolism, energy regulation, immune response and inflammation, and insulin sensitivity [1, 5].Adiponectin has insulin-sensitizing, anti-inflammatory, angiogenic, and vasodilatory properties, which may affect central nervous system (CNS) disorders [4, 9].Adiponectin contributes to the control of glucose uptake and lipids metabolism, by reducing gluconeogenesis and

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enhancing glycolysis and fatty acid oxidation in the liver [12].

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. According to the International Diabetes Federation (IDF), approximately 415 million adults between the ages of 20 to 79 years had diabetes mellitus in 2015[5, 2].

Type 2 diabetes mellitus (T2DM) is an insulin-resistance condition with associated beta-cell dysfunction [1, 8]. There is a compensatory increase in insulin secretion, which maintains glucose levels in the normal range. As the disease progresses, beta cells change, and insulin secretion is unable to maintain glucose homeostasis, producing hyperglycemia [30].

Diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) globally [8].DKD is characterized by albuminuria and reduced estimated glomerular filtration rate (eGFR), which are independent risk factors for end-stage kidney disease (ESKD), cardiovascular events, and death [5].

Insulin resistance is present even at earlier stages of CKD,[3] and its prevalence increases with further decline in kidney function [16]. Although the pathophysiology of insulin resistance in uremia has been recognized and explored over decades, evidence related to the effects of moderate CKD and adiposity in insulin resistance remains unsettled. The gold standard for diagnosing IR is the euglycemic hyperinsulinemic clamp test, which is the most informative direct diagnostic method with a high level of sensitivity and specificity [33].

Toll-like receptors (TLR) are found under the family of PRRs (Pattern recognition receptors) play an indispensable function in innate immunity and identify tissue injury by the danger-associated molecular patterns. Studies reported that, among the different types of TLR, TLR2 and TLR4 have a role in inflammation-associated insulin resistance during obesity [3,5]. In obese mice and humans with diabetes, the expression of TLR4 in adipocytes, hepatocytes, muscles, and in the hypothalamus is increased and negatively affects insulin sensitivity. Another study also revealed that, during obesity, metabolic endotoxemia triggers the development of inflammation and metabolic disorders by activating TLR4 in metabolic tissues[2, 8]. On the other hand, the abrogation of TLR4 leads to the reduction of oxidative stress by metabolic reprogramming of mitochondria in visceral fat, alleviating obesity-induced insulin resistance[1, 7]. In addition, various TLR inhibitors have been developed to regulate excessive inflammation; these are; small molecule inhibitors, antibodies, oligonucleotides, lipid-A analogs, microRNAs, and emerging nano-inhibitors[3].

Various markers are used to find out the pathological processes in obesity including cystatin-C (cys-C) as biomarkers of early stage renal diseases (ESRD)[12], and adiponectin as anti-inflammatory marker[2, 5]. Cys-C is a low molecular weight protein (13kD) which is an endogenous proteinase inhibitor produced by all nucleating cells in the human body at a fairly constant level. Cys-C is filtered freely by the glomerulus and almost completely reabsorbed in the proximal tubule. Cys-C is not affected by age, sex, muscle mass, ethnic and inflammatory conditions [3,7]. Cys-C is more appropriate for the determination of renal damage with a decrease in GFR than creatinine clearance. The National Kidney Foundation proposes to use cys-C to measure glomerular filtration rate (GFR) in a variety of clinical conditions in the youth population [2]. Cys-C is increased in obesity and is associated with GFR [6].

Cystatin C is an essential protein that is non-glycosylated and filtered by the glomerulus.It is considered as an indicator for evaluating renal function. Data suggest a potential genetic link between nonalcoholic fatty liver disease and chronic kidney disease in children. Studies on adults have reported a positive correlation between cystatin C level and body mass index (BMI) or waist circumference (WC). Further, some data suggested that increased cystatin C levels could be regarded as an early prognostic indicator of vascular risk in children with obesity .

Glomerular filtration rate (GFR) is the best routinely available estimate for kidney function and essential for detection and management of both acute kidney injury (AKI) and chronic kidney disease (CKD). Loss of kidney function by decreased estimated glomerular filtration rate (eGFR) is associated with poor survival [4]. Creatinine is the most frequently used biomarker for eGFR. Yet, creatinine may vary with factors not related to kidney function per se such as muscle mass, gender, ethnicity, and dietary factors [2,8]. Cystatin C is an alternative biomarker for eGFR-estimation which does not depend on muscle mass and thus fairly constant with age and gender [14]. Still, creatinine is the most frequently used estimate of eGFR in critically ill patients [2,9,13]. Patients in intensive care are ofen bedfast and may have loss of muscle mass and altered distribution volumes due to severe illness. An ongoing loss of muscle mass and low protein intake may possibly lead to a decrease in creatinine in plasma, leading to potential risk of eGFR overestimation [7,16]. It may therefore be

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hypothesized that creatinine is a less informative biomarker in the estimation of eGFR than cystatin C. Cystatin C may on the other hand be infuenced by cortisol, obesity and other traditional risk factors or possibly inflammation [5,14], which varies in critically ill.

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