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Research Progress on Novel Surrogate Indicators of Insulin Resistance in Type 2 Diabetic Kidney Disease

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Abstract: Diabetic kidney disease (DKD)is one of the most common and severe microvascular complications of type 2 diabetes mellitus (T2DM). It is also a major cause of end-stage renal disease (ESRD), making early identification and intervention crucial. Insulin resistance (IR)is a key pathophysiological mechanism of T2DM and plays a central role in the progression of DKD. In recent years, a series of novel surrogate indicators of IR, such as the triglyceride-glucose (TyG) index, TyG-body mass index (TyG-BMI), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), and metabolic score for insulin resistance (METS-IR), have attracted widespread attention due to their simplicity and cost-effectiveness. This article reviews the research progress of novel surrogate indicators of insulin resistance (IR) in type 2 diabetic kidney disease (DKD), aiming to provide references for the early prevention and improved prognosis of DKD.

Keywords: Insulin resistance; Type 2 diabetic kidney disease; Surrogate indicators; Review

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1. Introduction

The global burden of diabetes mellitus (DM)continues to increase due to factors such as population aging, urbanization, rising rates of overweight and obesity, sedentary lifestyles, and poor dietary habits. Diabetes and its complications have become a major public health challenge worldwide [1]. Diabetic kidney disease (DKD), as one of the most common microvascular complications of type 2 diabetes mellitus (T2DM), is clinically characterized by a persistent increase in albuminuria excretion and/or a progressive decline in the estimated glomerular filtration rate (eGFR) [2]. The International Diabetes Federation (IDF)released a report on Diabetes and Kidney Disease in December 2023, stating that up to 30–40% of diabetes patients will develop chronic kidney disease (CKD), with T2DM being the largest contributor to the diabetes-related CKD burden. Furthermore, diabetes remains the leading cause of renal failure or end-stage renal disease (ESRD)in adults [3]. However, the current treatment of DKD is mainly based on symptomatic drug therapy, and existing drugs are difficult to reverse its established pathological processes [4]. Therefore, the early identification and intervention of DKD have crucial clinical significance for delaying its progression and improving patient prognosis. Insulin resistance (IR), as one of the core pathophysiological mechanisms of T2DM, has been increasingly confirmed to be involved in the onset and progression of DKD in recent years [5,6]. Traditional methods for assessing IR mainly include:

(1) Hyperinsulinemic Euglycemic Clamp (HEC), which is regarded as the “gold standard” for identifying IR. However, it requires high operator proficiency, complex procedures, and is expensive, resulting in limitations in its clinical application [7].

(2) Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), which requires the measurement of serum insulin concentration and is mainly used in patients with T2DM. Moreover, the standardization of insulin measurement varies across different laboratories, making it difficult to achieve a uniform reference value [8,9].

Given these limitations, researchers have successively proposed a series of novel surrogate indicators of IR, including the triglyceride glucose (TyG) index, TyG-body mass index (TyG-BMI), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), and metabolic score for insulin resistance (METS-IR). These indicators are characterized by simple testing procedures and lower costs, showing promising application prospects in the general population. Therefore, this article aims to review the research progress of the above-mentioned novel surrogate indicators of IR in DKD.

2. Association between insulin resistance and diabetic kidney disease

IR serves as the common pathophysiological basis for a variety of chronic metabolic diseases, including T2DM, non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS) [10]. IR can induce renal injury through multiple pathways, mainly involving the following three aspects [11]:

(1) Hemodynamic changes

On the one hand, nitric oxide (NO) is an important vasoactive substance. IR leads to a reduction in NO production, which induces vasoconstriction and elevated blood pressure, impairs vascular endothelial cell function, and thus causes an increase in renal vascular resistance and a decrease in renal blood flow, ultimately resulting in a decline in eGFR. On the other hand, IR can stimulate the sympathetic nervous system and activate the renin-angiotensin-aldosterone system (RAAS), promoting the formation of a state of high pressure and hyperfiltration within the glomerulus and further exacerbating structural damage to the glomeruli.

(2) Oxidative stress

The IR state can activate oxidative stress, which promotes the proliferation and hypertrophy of mesangial cells, excessive deposition of the extracellular matrix, and thickening of the basement membrane. These changes lead to tubulointerstitial hypoxic injury and renal interstitial fibrosis, thereby accelerating the progression of DKD.

(3) Inflammatory response

IR can exacerbate the inflammatory response in patients with DKD, and its main mechanism involves a decrease in the levels of anti-inflammatory factors (such as adiponectin) and an increase in the levels of pro-inflammatory factors (such as leptin). Dysregulated levels of these inflammatory factors impair the renal protective effects and directly induce thickening of the glomerular filtration membrane and injury to the endothelial cells of glomerular capillaries.

In summary, IR promotes the development of DKD through the aforementioned multiple mechanisms and serves as a critical link in the progression of DKD.

3. Novel surrogate indicators of insulin resistance and diabetic kidney disease

3.1. TyG index

The TyG index was initially proposed by scholars such as Simental-Mendia, and its calculation incorporates two dimensions: glucose metabolism and lipid metabolism. Its calculation formula is: TyG = Ln [TG (mg/dL) × FPG (mg/dL)/2] [12]. Studies have confirmed that, compared to HEC, the TyG index exhibits high sensitivity and specificity in identifying reduced insulin sensitivity [13]. IR induces alterations in renal hemodynamics through various mechanisms, thereby contributing to the onset and progression of kidney disease. As a simple surrogate indicator of insulin resistance, the TyG index is significantly associated with the risk of DKD onset, albuminuria levels and the decline in eGFR. A cross-sectional and longitudinal analysis involving 1432 patients with T2DM indicated that patients with a higher TyG index had an increased risk of developing microalbuminuria. After adjusting for confounding factors, patients in the highest tertile of baseline TyG index had a higher risk of developing DKD than those in the lowest tertile, suggesting that the TyG index may serve as a potential predictive indicator for DKD in patients with T2DM [14]. Moreover, when comparing the correlation between proteinuria and insulin resistance in the T2DM population, the TyG index demonstrated the best diagnostic performance with an area under the curve(AUC) of 0.62 and a cut-off value of 9.39, outperforming other measurement indicators such as HOMA-IR [6]. In addition, the TyG index also demonstrates potential value in assessing cardiovascular and all-cause mortality among DKD patients. Based on the National Health and Nutrition Examination Survey (NHANES) database, Zhang et al. found that the TyG index is a key indicator for evaluating overall and cardiovascular mortality in DKD patients and revealed a nonlinear association with mortality. Therefore, utilizing the TyG index for individual risk assessment can provide new perspectives and help predict the risk of adverse outcomes in the DKD population [15]. However, most current studies on TyG for predicting DKD progression are cross-sectional in design, with relatively limited prospective studies. Furthermore, the specific mechanism underlying the association between the TyG index and DKD has not been fully elucidated, which warrants further investigation and exploration.

3.2. TyG-BMI

TyG-BMI was first proposed by Er et al [16]. It incorporates body mass index (BMI) on the basis of the TyG index, and is designed to reflect the synergistic effect of insulin resistance and obesity status, thus serving as a more comprehensive indicator. Its calculation formula is: TyG-BMI = TyG × BMI (kg/m^2). The study found that in identifying IR, the TyG-BMI had an AUC of 0.801, which was higher than that of the TyG index (AUC: 0.708), and it had a strong correlation with HOMA-IR. This suggests that the TyG-BMI has higher accuracy than the TyG index alone and can serve as a reliable predictor for IR [16]. Based on the longitudinal data from the China Health and Retirement Longitudinal Study (CHARLS), Deng et al. found that the sustained elevation of the TyG-BMI significantly increased the risk of developing diabetes. For each 10-unit increase in cumulative TyG-BMI, the risk of diabetes increased by 2.9%. This suggests that dynamic monitoring of changes in the TyG-BMI can provide critical evidence for early intervention of diabetes [17]. In terms of type 2 diabetic kidney disease, the higher the TyG-BMI, the greater the risk of developing early renal injury in patients with T2DM, and it acts as an independent risk factor for early renal injury in T2DM [4]. Jiang et al. found that, compared with the TyG index, the TyG-BMI demonstrated a more pronounced dose-response relationship with the risk of DKD, with an optimal cut-off value of 243, which is conducive to identifying the risk of DKD in newly diagnosed patients with T2DM [18]. Meanwhile, among individuals aged 45 and above with normal renal function in China, each 1-standard-deviation increase in the TyG-BMI was significantly associated with the onset of rapid kidney function decline(RKFD) and the progression of CKD [19]. However, the TyG-BMI relies on BMI, an obesity-related indicator, and struggles to reflect differences in fat distribution. Thus, its risk assessment capability may be limited in populations such as elderly patients, those with sarcopenia or high muscle mass. Future studies need to further investigate the applicability of the TyG-BMI in individuals with different body compositions and across different ethnic populations.

3.3. TG/HDL-C

The TG/HDL-C ratio was first proposed by McLaughlin et al., with its calculation formula as follows: TG/HDL-C = TG (mg/dL) ÷ HDL-C (mg/dL) [20]. Studies have found that dyslipidemia may already exist in the early stages of CKD, including elevated triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels [21]. In patients with T2DM, low HDL-C levels in the blood are significantly associated with the accelerated deterioration of renal function and an increased risk of mortality [22]. The TG/HDL-C ratio integrates dyslipidemia with the risk of IR into a single indicator. It does not require fasting insulin sampling and features ease of operation and low cost, thus demonstrating high practical utility in routine clinical practice. A study involving 3739 participants undergoing routine health check-ups found that an elevated TG/HDL-C ratio was closely associated with abnormal albuminuria and exhibited a certain predictive value for albuminuria [23]. Zhang et al. found that the TG/HDL-C ratio was higher in patients with early renal injury secondary to T2DM than in those with early renal injury without diabetes. After stratifying the study population by TG/HDL-C quartiles and adjusting for confounding factors, the results showed that a higher TG/HDL-C ratio was associated with an increased risk of early renal injury in T2DM patients, indicating that the TG/HDL-C ratio is an independent risk factor for early renal injury in T2DM [4]. All the above findings indicate that the TG/HDL-C ratio holds important reference value for reflecting the body's lipid metabolism status and identifying early renal injury, suggesting that in clinical practice, this study can utilize blood lipid profiles, a simple and readily measurable indicator, to explore targeted intervention strategies guided by the TG/HDL-C ratio for reducing the risk of diabetes mellitus and its related complications. Nevertheless, the molecular pathways by which the TG/HDL-C ratio contributes to DKD progression remain to be elucidated by additional basic and clinical studies. Furthermore, the TG/HDL-C ratio is highly influenced by dietary patterns, lipid-lowering drugs, and ethnic differences, and the optimal cut-off values have not been standardized across diverse populations, which results in certain limitations in its application for DKD risk prediction.

3.4. METS-IR

METS-IR was first proposed by the Mexican scholar Bello-Chavolla et al. in 2018. In comparison with traditional surrogate indicators of IR, METS-IR integrates three key dimensions: glucose metabolism (such as FPG), lipid metabolism (such as HDL-C), and body composition (such as BMI), and thus can reflect the metabolic status more comprehensively than a single indicator. Its calculation formula is as follows: METS-IR = Ln [2 × FPG (mg/dL) + TG (mg/dL)] × BMI (kg/m^2) ÷ Ln [HDL-C (mg/dL)] [24]. At present, research on METS-IR has mainly focused on mortality prediction, association studies with metabolic diseases, comparative studies on index efficacy, and preliminary investigations into relevant pathological mechanisms. A higher METS-IR is significantly associated with an increased risk of T2DM in non-obese populations, suggesting that METS-IR may serve as a reliable indicator for screening individuals at high risk of early T2DM [25]. Meanwhile, as a surrogate indicator of IR, METS-IR is closely associated with pathological processes in the kidney such as hemodynamic changes and oxidative stress. A study investigating the association between METS-IR and eGFR in Japanese participants undergoing routine health check-ups found that METS-IR was significantly associated with eGFR: for every 10-unit increase in METS-IR, eGFR decreased by 2.54 units. This suggests that METS-IR can serve as a monitoring indicator for the early screening, prevention and diagnosis of CKD [26]. A cross-sectional study based on 6891 patients with diabetes mellitus demonstrated a significant association between METS-IR and the risk of DKD. After adjusting for several covariates including gender, age, and ethnicity, this association remained statistically significant [27]. However, variations exist in the calculation formulas and adjusted variables of METS-IR across different studies, and its relatively complex calculation has to some extent hindered its clinical application and popularization. Furthermore, specific research on the association between METS-IR and DKD is still lacking, and its role in the diagnosis of DKD has not yet been investigated. More clinical studies are therefore needed in the future to explore and validate the correlation and predictive value of METS-IR for DKD.

4. Conclusion

Through a review of studies on four novel surrogate indicators of IR in DKD, this paper provides a more comprehensive understanding of the research value of these indicators and their associations with DKD. Current studies suggest that these indicators, holding potential value for early risk identification and stratified management in clinical practice, are associated with the onset and progression of DKD as well as renal function impairment. However, existing research in this field is mostly limited to cross-sectional studies or retrospective analyses, and the optimal cut-off values, long-term predictive efficacy of each indicator, as well as their specific pathophysiological mechanisms, have not been fully elucidated to date. Therefore, more multi-center, prospective cohort studies and in-depth mechanistic explorations are needed in the future to further validate the clinical value of these indicators. In addition, combined with traditional renal indicators and new biomarkers, a comprehensive risk assessment model should be constructed to promote its integration into the standardized prevention and treatment system of DKD. In summary, the novel surrogate indicators of IR are expected to become effective tools for clinicians to conduct early screening of high-risk groups for DKD, perform risk stratification and implement timely intervention, which is of great clinical significance for delaying the progression of DKD and improving the prognosis of patients.

Disclosure statement

The authors declare no conflict of interest.

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