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COMMENT

Indicators of insulin resistance in clinical practice

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Hypertension and cardiovascular disease (CVD) are global health concerns. Insulin resistance, defined as a decreased response to insulin in target tissues, is a pathological condition that underpins hypertension and CVD. It is thought to play a significant role in their development. Therefore, measuring insulin resistance may help evaluate the risk of hypertension and CVD. However, the gold standard for assessing insulin resistance, namely, the glucose clamp technique, is an expensive and complicated procedure that makes it difficult for clinical practice and thus used only in experiments and small-scale studies. Therefore, a number of surrogate markers for insulin resistance have been proposed, including the homeostasis model assessment of insulin resistance (HOMA-IR) [1] and Matsuda index. Most large-scale studies have used HOMA-IR because it is obtained using a simple formula based only on fasting blood glucose and insulin levels. However, the association between the insulin resistance index and hypertension and cardiovascular risk remains inconclusive [2]. As a result, the assessment of insulin resistance has not yet become a definitive tool for predicting cardiovascular risk in clinical practice.

Recently, two new developments in clinically available indicators of insulin resistance have emerged (Fig. 1). One is the establishment of an indicator of insulin resistance in adipose tissue, called "adipose insulin resistance index (Adipo-IR)," which is calculated as the product of fasting insulin and fasting free fatty acid (FFA) levels [3]. Traditional insulin resistance indices, such as HOMA-IR, Matsuda index, and glucose clamp technique parameters, were calculated using serum insulin and glucose levels. Although insulin performs various functions in different tissues, these indices are only indicators of the efficiency of insulin-induced glucose uptake in the target organ (primarily the liver and skeletal muscle). Adipo-IR is based on the idea that insulin regulates serum FFA levels by inhibiting lipolysis, which is the synthesis of FFA and glycerol from triglycerides in adipose tissue. Adipo-IR was associated not only with glycemic status but also with serum adipokine levels, such as leptin and adiponectin [4], and the incidence of dyslipidemia [5] and hypertension [6]. Given the importance of obesity in the development of hypertension and CVD, adipo-IR could be a useful insulin resistance marker in clinical practice. The other is a cost-effective indicator of insulin resistance that does not require insulin measurement, such as the triglyceride glucose (TyG) index and triglycerides/high-density lipoprotein cholesterol ratio. Insulin resistance is accompanied by compensatory hyperinsulinemia, which may activate the sympathetic nervous system and renin–angiotensin system, and cause renal sodium retention. All these effects may contribute to the cross-sectional association between serum insulin levels and blood pressure. However, independent of insulin resistance, the long-term adverse cardiovascular effects of hyperinsulinemia per se have yet to be established [7]. Several experimental studies have found that chronic hyperinsulinemia reduces peripheral vascular resistance [8], and it has no or only a minor effect on blood pressure elevation progression [9]. Therefore, excluding serum insulin values as the basis for calculations does not necessarily reduce its clinical utility as an indicator of insulin resistance.

In the current issue of *Hypertension Research*, Miao et al. [10] used the TyG index, which is calculated using only fasting blood glucose and triglyceride values. In addition to being inexpensive, the TyG index has been shown to be highly correlated with the insulin resistance

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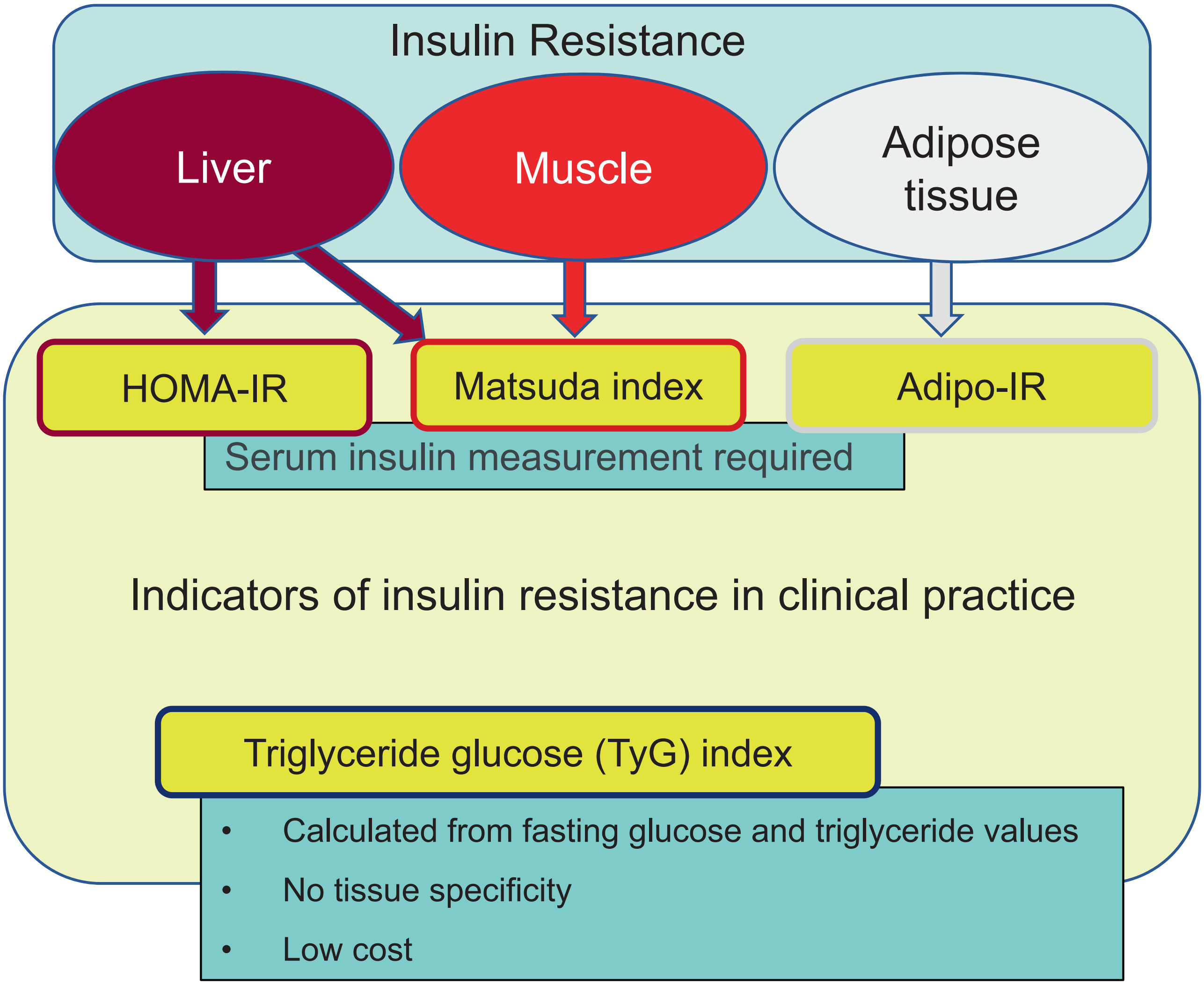
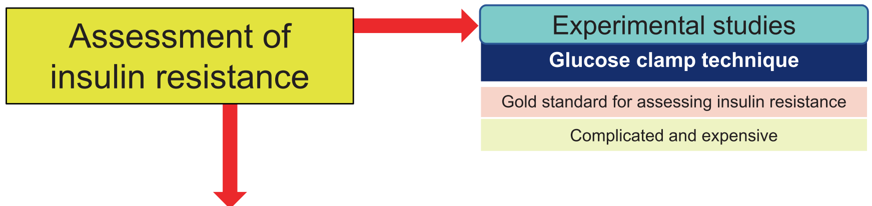
Graphical Opinion



index obtained from the euglycemic–hyperinsulinemic clamp test [11]. Several studies have found a link between TyG and arterial stiffness, coronary artery calcification, hypertension, and CVD risk [12, 13]. In the current study, Miao et al. [10] investigated the association between the TyG index and combined TyG and anthropometric indicators (i.e., TyG-body mass index, TyG-waist circumference, TyG waist–hip ratio, and TyG waist–height ratio) with the prevalence of hypertension and CVD risk in a Chinese population. All the TyG index and TyG-related parameters were significantly associated with hypertension and CVD risk after adjusting for confounding factors. They demonstrated that the TyG-waist circumference was superior to the TyG index and was the best among all TyG-related parameters for the diagnosis of hypertension. Similarly, the TyG-waist–hip ratio was superior to the TyG index and was the best among all parameters related to TyG in terms of association with CVD risk. These results suggest that the TyG index's ability to predict hypertension and CVD risk may be improved by modification using anthropometric indicators. Therefore, this study is an important attempt to increase the clinical significance of the TyG index without increasing the cost. However, this study had some limitations. First, because this study used a cross-sectional research design, the results will need to be validated in future longitudinal studies. Second, unlike the HOMA-IR and Adipo-IR indices, the TyG index is not based on specific insulin action. The levels of serum triglycerides and skeletal muscle triglycerides may be involved in muscle insulin resistance [14, 15], but to what extent this contributes to the mechanism by which the TyG index reflects insulin resistance remains unclear. Therefore, the precise mechanism by which each anthropometric metric improves the TyG index's ability is also unclear.



Large-scale studies

	HOMA-IR	Matsuda index	Adipo-IR	TyG index
Fasting glucose	✓	✓		✓
Fasting insulin	✓	✓	✓	
Fasting FFA			✓	
Fasting TG				✓
Oral glucose tolerance test		✓		
Tissue specificity	Liver	Liver + Muscle	Adipose tissue	N/A
Rationale	Insulin-induced glucose uptake in the target organ	Insulin-induced glucose uptake in the target organ	Insulin-induced inhibition of lipolysis	Increased TG and glucose levels due to insulin resistance
Cost	Medium	High	Medium	Low

Fig. 1 Indicators of insulin resistance. Adipo-IR adipose insulin resistance index, FFA free fatty acid, HOMA-IR homeostasis model assessment of insulin resistance, TG triglyceride, TyG index triglyceride glucose index

Identifying high-risk individuals for hypertension and CVD is critical in clinical practice because early intervention, such as lifestyle changes, can prevent these diseases and improve prognosis. In this regard, low-cost insulin resistance indicators appear to be a promising tool, and future research is expected to advance.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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