Understanding Mechanisms of Insulin Resistance in Diabetes and Obesity

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Abstract**—**Insulin resistance in insulin target tissues including liver, skeletal muscle and adipose tissue is an early step in the progression towards type 2 diabetes. Accurate diagnostic parameters reflective of insulin resistance are essential. Longstanding tests for fasting blood glucose and HbA1c are useful and although hyperinsulinemic euglycemic clamp remains a 'gold standard' for accurately determining insulin resistance, it cannot be implemented on a routine basis. The study of adipokines, and more recently myokines and hepatokines, as potential biomarkers for insulin sensitivity is now an attractive and relatively straightforward approach. This review discusses potential biomarkers including adiponectin, RBP4, chemerin, A-FABP, FGF21, fetuin-A, myostatin, IL-6, and irisin, all of which may play significant roles in determining insulin sensitivity. We also review potential future directions of new biological markers for measuring insulin resistance, including metabolomics and gut microbiome. Collectively, these approaches will furnish clinicians with the armoury for more accurate, and perhaps personalized, diagnosis of insulin resistance.

Keywords—Obesity, Diabetes, Adipokines, Biomarker, Therapeutic target.

I. Introduction

INSULIN resistance is often regarded as the primary cellular defect in the development of type 2 diabetes (1, 2). Ultimately, the combination of insulin resistance, subsequent hyperinsulinemia followed by hypoinsulinemia lead to hyperglycemia and the development of complications associated with diabetes. However, although insulin resistance begins before the onset of overt disease, it has proven somewhat difficult to accurately assess in routine clinical practice. Thus, the vital clinical importance of having accurate diagnostic parameters reflective of insulin resistance has generated decades of research in this area aimed at developing new diagnostic tools (1).

Insulin resistance is a key feature of these diseases and is defined as a state that requires more insulin to obtain the biological effects achieved by a lower amount of insulin in the normal state. Thus, although a simple oral glucose test is often used as a diagnostic tool for type 2 diabetes, it is not a good measure of insulin resistance. Accurate evaluation of insulin resistance is of course possible by clinical examinations such as hyperinsulinemic euglycemic clamp, which is regarded as the 'gold standard' for determining insulin resistance, or a modified insulin suppression test (3). However, the complicated nature of these techniques which need to be performed in a clinical setting and carry the inherent potential danger of hypoglycemia limits their routine use. A commonly used alternative test was the Homeostatic Model Assessment (HOMA) (4), and more recently the Quantitative Insulin Sensitivity Check Index (QUICKI) was developed (5). Both methods use fasting insulin and glucose concentrations to assess insulin resistance and correlate reasonably well with the results of clamp studies. These laboratory diagnoses are also fast, easy and unobtrusive to the patient. However, neither HOMA or QUICKI are able to detect early stage insulin resistance and the emphasis has recently shifted to establishing biomarkers which will achieve this goal (6, 7).

The US Food and Drug Administration defines a *biomarker* as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or biological responses to a therapeutic intervention. Based upon recent advances from basic research enhancing our understanding of the molecular mechanisms of insulin resistance, numerous potential biomarkers have been identified (6, 7). Thus, here we review the current and potential future use of biomarkers as an alternative for determining the insulin resistance status.

II. Current clinical biomarkers of insulin resistance

One of the major dogma in the pathogenesis of insulin resistance associated with obesity or inflammation, is that the profile of adipokines secreted by adipose tissue is altered (8). These adipokines have autocrine, paracrine and endocrine actions both directly on metabolism as well as on insulin sensitivity (9, 10). Accordingly, they have become very attractive candidates for routine analysis of insulin sensitivity by simply measuring their circulating levels in blood. Although adipokines are the most well known organokines, other classes of organokines including myokines, cardiokines and hepatokines have been identified; and perhaps underappreciated to date (10). Recently, many studies have established the complex role, and interplay, of organokines in determining insulin sensitivity in various tissues. In this review, we summarize several of the major organokines which are currently proposed as useful biomarkers for evaluating insulin resistance.

III. Adipokines as biomarkers of insulin resistance

Numerous adipokines have a well established important role in the development of obesity-related comorbidities (8, 11).

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Here we briefly summarize background information and study of adiponetcin as a potential biomarker for insulin resistance.

IV. Adiponectin

Among the multitude of adipokines, adiponectin is a highly abundant plasma protein synthesized predominantly in adipose tissue. Adiponectin shares structural homology with complement factor C1q and has a long collagenous domain and a globular head. It undergoes complex posttranslational processing, oligomerizing into trimers, hexamers, and high molecular weight (HMW) multimers by means of disulfide bonding (12). A huge number of publications in humans, animal models, isolated tissues and cultured cell types have determined that adiponectin enhances peripheral insulin sensitivity and also mediates anti-inflammatory, anti-atherosclerotic and cardioprotective effects, all of which have been extensively reviewed (13, 14). Adiponectin's physiological effects are mediated primarily through two adiponectin receptors (AdipoR) with seven membrane spanning domains, although these are not G-protein coupled. Instead, these receptors link via several adaptor proteins to downstream signaling events, amongst which activation of AMPK, p38MAPK, PPARα, PPARγ are of particular significance (15). The adiponectin binding protein T-cadherin has also been implicated in mediating effects of adiponectin (16).

Most clinical correlative studies have employed immunoassays of total adiponectin and shown an inverse correlation with insulin resistance (14, 17, 18). Additional studies which have discriminated between the oligomeric forms indicated that it is the HMW form that correlates most strongly with various features of the metabolic syndrome (19). Circulating total adiponectin strongly and reproducibly correlates with markers of insulin resistance, whether they are derived from fasting data alone, from oral glucose tolerance testing or from hyperinsulinemic euglycemic clamp studies (20). In summary, many clinical studies clearly indicate that adiponectin could act as a potential biomarker for insulin resistance. These, together with evidence from animal models and in vitro analyses which indicate that adiponectin exerts insulin-like or insulin-sensitizing metabolically beneficial effects (14, 17, 18), also make adiponectin an attractive therapeutic target (21). Accordingly, numerous dietary factors and current therapeutics have been shown to act at least in part by elevating circulating levels or expression of its receptors, thus improving insulin sensitivity (21). Importantly, an orally active small molecule Adiponectin receptor agonist was recently characterized as an effective therapeutic approach for the treatment of insulin resistance and type 2 diabetes, so far in animal models (22).

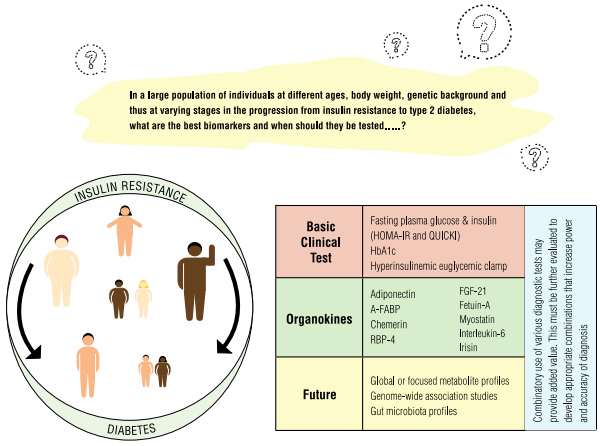

Fig. 1 A schematic summary of current basic clinical tests, organokine-based diagnostics and potential future biomarkers for insulin resistance. These can all be applied in testing a diverse population of patients worldwide

V. Conclusions

A good biomarker should be easy to measure, provide valuable information about insulin resistance, display good reproducibility and precision, and have a good cost-to-effectiveness ratio. Numerous biomarkers of insulin resistance have been proposed (figure 1) and the text above highlights the caveats associated with many of these, meaning that a robust and unequivocal test is hard to establish. Perhaps this is not surprising given the diverse pathogenesis of insulin resistance and diabetes. An important emerging hypothesis is that combinations of well established biomarkers are likely to confer more power in terms of accurately gauging the degree or indeed likely development of insulin resistance. In fact, multivariate models have been proposed based on multiple protein biomarkers for identifying individuals with high levels of insulin resistance. Thus, combinatorial biomarker analyses in a more personalized manner may prove to be the most reliable diagnostic format. Patient to patient variability can also be a confounding factor when using organokines in clinical diagnostics, but nevertheless we believe that adiponectin, FGF-21 and lipocalin-2 may hold most value. In summary, although organokines as biomarkers is an attractive concept due to convenience and speed, the absolute accuracy is mostly inferred and the accuracy may not apply equally in all individuals. Additional research and clinical analyses to establish significant interdependencies between proteins must be conducted.

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