TOPIC HIGHLIGHT

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Surrogate markers of insulin resistance: A review

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Abstract

Insulin resistance is a hallmark of obesity, diabetes, and cardiovascular diseases, and leads to many of the abnormalities associated with metabolic syndrome. Our understanding of insulin resistance has improved tremendously over the years, but certain aspects of its estimation still remain elusive to researchers and clinicians. The quantitative assessment of insulin sensitivity is not routinely used during biochemical investigations for diagnostic purposes, but the emerging importance of insulin resistance has led to its wider application research studies. Evaluation of a number of clinical states where insulin sensitivity is compromised calls for assessment of insulin resistance. Insulin resistance is increasingly being assessed in various disease conditions where it aids in examining their pathogenesis, etiology and consequences. The hyperinsulinemic euglycemic glucose clamp is the gold standard method for the determination of insulin sensitivity, but is impractical as it is labor- and time-intensive. A number of surrogate indices have therefore been employed to simplify and improve the determination of insulin resistance. The object of this review is to highlight various aspects and methodologies for current and upcoming measures of insulin sensitivity/resistance. In-depth knowledge of these markers will help in better understanding and exploitation of the condition.

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INTRODUCTION

Insulin is a key regulator of glucose homeostasis. Insulin resistance is established by genetic and environmental factors. Insulin resistance (IR) leads to impaired glucose tolerance, and plays an important pathophysiological role in the development of diabetes[1]. In addition, IR leads to many of the metabolic abnormalities associated with metabolic syndrome/syndrome X. Patients with insulin resistance are likely to have impaired fasting plasma glucose levels, which in turn enhance the prevalence of more atherogenic, small dense low-density lipoprotein (LDL) particles. Central obesity and insulin resistance form the basis of the pathophysiology of dyslipidemia, lack of glucose tolerance, and the existence of chronic subclinical inflammation and hypertension in metabolic syndrome. IR has been described as a condition where a greater than normal amount of insulin is required to obtain a quantitatively normal response[2]. Measuring

IR: PATHOGENESIS

The mechanism underlying IR involves a complex network of metabolism of glucose and fat, with the inflammatory cascade playing an important role. The important actions of insulin are anti-lipolysis in adipose tissue and stimulation of lipoprotein lipase[3]. Expanded adipose tissue mass associated with obesity mobilises free fatty acids (FFA) in circulation through the action of the cyclic-AMP dependent enzyme hormone sensitive lipase. FFA are also released through lipolysis of Triglyceride (TG)-rich lipoproteins in tissues by means of lipoprotein lipase[4]. In insulin-sensitive tissue, excessive fatty acids create insulin resistance by means of the added substrate availability and by modifying down- stream signalling[5]. When insulin resistance sets in, the increased lipolysis of stored TG in adipose tissue produces more fatty acids. The increased FFA concentration inhibits the anti-lipolytic action of insulin. The role of innate immunity and infection has also been postulated in the development of insulin resistance and can predict the development of diabetes mellitus type II [6,7].

Insulin resistance, metabolic syndrome and atherosclerotic events share a common inflammatory basis. Presence of a low-grade systemic inflammation is the main mechanism that leads to impaired insulin action[8].

DISEASE CONDITIONS ASSOCIATED WITH IR

IR is an important clinical and biochemical determinant, not only of diabetes but also of many other clinical states. There is a need to evaluate insulin resistance, since it is an underlying mechanism and predictor of cardio-vascular diseases, diabetes, hypertension, obesity and other consequences of metabolic syndrome and impaired insulin sensitivity. In nondiabetic individuals, the initial presentation associated with insulin resistance is hyperinsulinemia, impaired glucose tolerance, dyslipidemia [hypertriglyceridemia and decreased high-density lipoprotein (HDL) cholesterol] and hypertension[9]. Insulin resistance contributes significantly to the pathophysiology of type 2 diabetes and is a hallmark of obesity, dyslipidemias, hypertension, and other components of the metabolic syndrome[10,11]. The association between insulin resistance and subclinical or clinical cardio-vascular disease in both nondiabetic[12-14] and diabetic subjects[15,16] has been observed.

Insulin resistance has been an area of interest in recent times, as it has effects on wide array of diseases. The pathophysiological conditions coupled with insulin resistance have persistently increased and include small dense LDL particles[17], augmented postprandial lipemia[18], enhanced renal sodium retention and high uric acid levels[19], dysfibrinolysis[20] increased resting heart rate[21] and polycystic ovarian syndrome[22]. In clinical practice, a family history of diabetes, a history of polycystic ovarian syndrome, gestational diabetes, impaired glucose metabolism, and obesity should be seen as a herald of the possibility of insulin resistance[23].

ESTIMATION OF IR/MEASUREMENT OF IR

A marker is a measurable variable found in an available biological sample or detected by tissue imaging, which can reflect the underlying disease pathophysiology, predict future events and indicate the response to treatment. Markers serve as sensitive detectors of early target organ damage[24]. Currently, validated risk-assessment tools do not satisfactorily account for the increased risk factors associated with metabolic syndrome[25]. Hence the need to identify markers of this syndrome is imperative.

Estimation of insulin resistance is being studied widely in humans. It is of great importance to develop animal models that are appropriate to the investigation of the epidemiology, pathophysiological mechanisms, outcomes of therapeutic interventions, and clinical courses of patients with insulin resistance. Insulin resistance is an established independent predictor of a range of disorders. Resistance to insulin sets in long before any disease signs start appearing. It is important to categorize and treat individuals with insulin resistance as early as possible, because hyperinsulinemia might remain undiagnosed for a long period, thereby increasing the risk of the development of other components of the syndrome, and consequent diseases. Prompt recognition and management of this metabolic syndrome offers important preventive measures[23].

In addition to maintaining whole body glucose homeostasis and promoting efficient glucose utilization[26], there are many other important physiological targets of insulin, including the brain, pancreatic β-cells, heart and vascular endothelium, that help to coordinate and couple metabolic and cardiovascular homeostasis under healthy conditions[26-29]. An accurate method for easily evaluating insulin sensitivity and following changes after therapeutic intervention is thus required.

NEED FOR SURROGATE MARKERS

Quantifying insulin sensitivity/resistance in humans and animal models is of great importance for basic science investigations and eventual use in clinical practice[30].

Among the tools to characterize IR and measure whole-body insulin action, the euglycemic hyperinsulinemic clamp technique is the direct method of estimation of IR. As this requires insulin infusion and repeated blood sampling, there is a need for simple, accessible measures for the evaluation of insulin sensitivity. Most large scale epidemiological studies merely correlate fasting insulin levels with the concerned outcome.

Table 1 Various methods to measure insulin resistance

S No	Method	Comments	Advantages	Disadvantages
1	Hyperinsulinemic euglycemic glucose clamp	Gold standard method for quantifying insulin sensitivity	Direct measure of insulin under steady-state conditions	Laborious, involves intra venous infusion of insulin, frequent blood sampling
2	Oral glucose tolerance test	Clinically used to detect glucose intolerance	Helps in estimating other surrogate indices	Useful for glucose tolerance but not for IR
3	Fasting insulin	Most practical method to measure IR	Detects insulin resistance before clinical disease appears	Lack of standardization of the insulin assay procedure
4	Glucose/insulin ratio (G/I ratio)	comparable to insulin sensitivity measured by the FSIVGTTT	Highly sensitive & specific for insulin sensitivity	Does not aptly reveal the physiology of insulin sensitivity
5	Insulinogenic index (IGI)	index of β-cell function δI (0-30 min)/δG (0-30 min)	Measure of first-phase insulin response to glucose challenge	Not broadly validated
6	Homeostasis model assessment	Assesses inherent β-cell function and insulin sensitivity $HOMA\text{-}IR = (G \times I)/22.5$	Simple, minimally invasive, predicts fasting steady-state G and I levels	Insulin sensitivity in subjects treated with insulin needs further validation
7	Quantitative insulin sensitivity check index (QUICKI)	Mathematical transformation of FBG and insulin $QUICKI = 1/[log (I \mu U/mL) + log(G mg/dL)]$	Consistent, precise index of insulin sensitivity, minimally invasive	Normal range to be established for each laboratory due to significant inter laboratory variations in insulin assay
8	Minimal model analysis of frequently sampled intravenous glucose tolerance test	Indirect measure of insulin sensitivity/resistance	Analysis using the computer program MINMOD	Multiple blood sampling
9	Glucose insulin (GI) product	Index of whole-body insulin sensitivity		
10	Fasting insulin resistance index (FIRI)	(fasting G × fasting I)/25		

G: Glucose; I: Insulin; IR: Insulin resistance; FBG: Fasting blood glucose.

IR can be assessed by various means. Most of the methods employed are difficult to apply in clinical practice. Since compensatory hyperinsulinemia is highly correlated with IR[31], it has been observed that it may offer a better way to identify insulin-resistant patients than do measurements of glucose intolerance. On the other hand, analytic methods for insulin measurements are not standardized, thus making it hard to compare absolute values of plasma insulin concentrations from one laboratory to another[32].

There has been an urgent need for the consideration of other parameters that can be used to assess IR, along with the development of novel surrogate markers of insulin resistance, which are more applicable for large population-based epidemiological investigations. Numerous such markers have been proposed on many occasions in the literature[33-39].

More than 15 years ago, the mathematical model of the normal physiological dynamics of insulin and glucose produced the homeostasis model assessment (HOMA), which provided equations for estimating insulin resistance (HOMA-IR) and β-cell function from simultaneous fasting measures of insulin and glucose levels[36]. AIn addition, the quantitative insulin sensitivity check index (QUICKI) derived from logarithmically-transformed fasting plasma glucose (FPG) and insulin levels has proven to be a first-rate index of insulin resistance in comparison with clamp-IR[40].

The efficacy and implication of surrogate assessment of insulin resistance depends on the extent to which it correlates with the direct estimate of this variable.

Various methods to quantify insulin resistance have been described, and are shown below in Table 1.

Hyperinsulinemic euglycemic glucose clamp

The hyperinsulinemic euglycemic glucose clamp technique has been described as the gold standard method for quantifying insulin sensitivity[41]. It is the reference method for quantifying insulin sensitivity in humans because it directly measures the effects of insulin in promoting glucose utilization under steady-state conditions *in vivo*[41]. Direct estimation of IR by means of the euglycemic clamp technique and insulin suppression test (IST) is experimentally demanding, complicated, and impractical when large scale epidemiological studies are involved. These methods are laborious, painstaking and expensive, are therefore rarely used in larger-scale clinical research and, as such, are irrelevant for clinical practice. Consequently, over the years, a number of surrogate indices for insulin sensitivity or insulin resistance have been developed.

The glucose clamp is difficult to apply in large scale investigations because of the chaotic procedure, which involves intra-venous infusion of insulin, taking frequent blood samples over a 3 h period, and the continuous adjustment of a glucose infusion.

SURROGATE MARKERS

Oral glucose tolerance test

The oral glucose tolerance test (OGTT) is an easy test,

and is commonly used in medical practice to detect glucose intolerance as well as type 2 diabetes[42]. It involves the administration of glucose to find out how rapidly it is cleared from the blood stream. It implicates the efficiency of the body to utilize glucose after glucose load.

During OGTT, after 8 to 10 h of fasting, blood glucose levels are determined at 0, 30, 60, and 120 min following a standard oral glucose load (75 g)[42,43].

It imitates the normal physiology of the glucose and insulin flux more closely than conditions of the other methods such as the glucose clamp, IST, or the Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT). Since glucose tolerance and insulin sensitivity are dissimilar conceptually, OGTT provides useful information about glucose tolerance but not insulin resistance. However, OGTT is also used to estimate other surrogate indices of insulin resistance. Impaired glucose tolerance offers few aberrations during OGTT. Firstly, rapid and continuous rise in plasma glucose concentration, and secondly, lack of decline below 140 mg/dL in plasma glucose at 2 h after attaining peak value. Subjects with impaired fasting glucose (IFG) have higher FPG than individuals with normal glucose tolerance or impaired glucose tolerance (IGT)[44].

Fasting insulin

Measurement of the fasting insulin level has long been considered the most practical approach for the measurement of insulin resistance[33]. It correlates well with insulin resistance. A considerable correlation has been found between fasting insulin levels and insulin action as measured by the clamp technique. A substantial overlap between insulin-resistant and normal subjects is a constraint, as there is a lack of standardization of the insulin assay procedure. Nevertheless, with a reliable insulin assay, insulin resistance can be detected early, before clinical disease appears[45].

As glucose levels change rapidly in the postprandial state, the use of fasting insulin for estimating IR should be done after an overnight fast, since the variable levels of glucose confound the simultaneous measure of insulin.

In healthy subjects, increased fasting insulin levels (with normal fasting glucose levels) correspond to insulin resistance. In this population 1/(fasting insulin) can substituted for insulin sensitivity that decreases as subjects become more insulin resistant (and fasting insulin levels rise)[33]. However, it does not cover the inappropriately low insulin secretion in the face of hyperglycemia seen in diabetic subjects or glucose-intolerant subjects.

Use of fasting insulin levels for assessment of IR is limited because of a high proportion of false-positive results and by lack of standardization. To overcome this issue, standardization of insulin assay has been recommended by the ADA Task Force, to be certified by a central laboratory[44].

A high plasma insulin value in individuals with normal glucose tolerance reflects insulin resistance, and high insulin levels presage the development of diabetes[45].

Glucose/insulin ratio

The Glucose/insulin (G/I) ratio has been employed in a number of studies as an index of insulin resistance[34,46,47]. Functionally, it will be equivalent to 1/(fasting insulin) in non- diabetics as fasting glucose levels are all in the normal range, though it does not appropriately reflect the physiology underlying the determinants of insulin sensitivity[48]. The fasting G/I ratio is a theoretically imperfect index of insulin sensitivity.

In a study conducted by Legro *et al*[35] fasting G/I ratio was compared to insulin sensitivity measured by the FSIVGTT. It was found that fasting G/I ratio is a highly sensitive and specific measurement of insulin sensitivity.

Insulinogenic index

The insulinogenic index (IGI) is a frequently used index of β-cell function. It is an index of insulin secretion derived from OGTT[49].

IGI = δinsulin (0-30 min)/δglucose (0-30 min)

Insulin is measured in microunits per millilitre, whereas glucose is measured in milligrams per decilitre[49].

The insulinogenic index helps to estimate the level of insulin secretion with a more physiological route of glucose administration.

While it has not been extensively validated,the insulinogenic index during the first 30 min of the OGTT has commonly been used in epidemiological studies as a surrogate measure of first-phase insulin responses to a glucose challenge.

HOMA

HOMA was first developed in 1985 by Matthews *et al*[36]. It is a method used to quantify insulin resistance and beta-cell function from basal (fasting) glucose and insulin (or C-peptide) concentrations. HOMA is a model of the relationship of glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β-cell function. Insulin levels depend on the pancreatic β-cell effect to glucose concentrations while, glucose concentrations are regulated by insulin-mediated glucose production via the liver. Thus, deficient β-cell function will echo a diminished response of β-cell to glucose-stimulated insulin secretion[35,50,51]. Similarly, insulin resistance is reflected by the diminished suppressive effect of insulin on hepatic glucose production. The HOMA model has proved to be a robust clinical and epidemiological tool for the assessment of insulin resistance.

HOMA describes this glucose-insulin homeostasis by means of a set of simple, mathematically-derived nonlinear equations. The approximating equation for insulin resistance has been simplified, and uses a fasting blood sample. It is derived from the use of the insulin-glucose product, divided by a constant. The product of FPG × FPI is an index of hepatic insulin resistance.

HOMA-IR = (glucose × insulin)/22.5: Insulin concentration is reported in μU/L and glucose in mmol/L.

The constant of 22.5 is a normalizing factor; i.e, the product of normal fasting plasma insulin of 5 μU/mL, and the normal fasting plasma glucose of 4.5 mmol/L typical of a "normal" healthy individual = 22.5. Whereas the β-cell function is also calculated by another equation using fasting insulin and glucose values.

HOMA1 - %B = (20 × FPI)/(FPG - 3.5): On the other hand, HOMA β-cell is another calculated variable indicating the insulin activity. It is a marker of basal insulin secretion of pancreatic β-cells[52].

HOMA β cell = 20 × fasting plasma insulin (μU/mL)/FPG (mmol)-3: Estimation with the help of HOMA model parallels equally with that of the euglycemic clamp method ($r = 0.88$)[51].

HOMA-IR has been observed to have a linear correlation with the glucose clamp and minimal model estimates of insulin sensitivity/resistance in various studies of distinct populations[51,53]. Derived from a mathematical assessment of the interaction between β-cell function and IR, the HOMA model is used to compute steady-state insulin and glucose concentrations. C-peptide, a measure of insulin secretion (not insulin action), can be used in HOMA modelling of both β-cell function and IR.

QUICKI
QUICKI is an empirically-derived mathematical transformation of fasting blood glucose and plasma insulin concentrations that provides a consistent and precise index of insulin sensitivity with better positive predictive power[41,54-56]. It is simply a variation of HOMA equations, as it transforms the data by taking both the logarithm and the reciprocal of the glucose-insulin product, thus slightly skewing the distribution of fasting insulin values.

QUICKI has been seen to have a significantly better linear correlation with glucose clamp determinations of insulin sensitivity than minimal-model estimates, especially in obese and diabetic subjects[54]. It employs the use of fasting values of insulin and glucose as in HOMA calculations. QUICKI[37] is virtually identical to the simple equation form of the HOMA model in all aspects, except that a log transform of the insulin glucose product is employed to calculate QUICKI.

QUICKI = 1/[log (Insulin μU/mL) + log (Glucose mg/dL)][37].

QUICKI should not be considered, as a new model rather simply logs HOMA-IR, which explains the near-perfect correlation with HOMA. It has similar drawbacks to the use of the HOMA equations, compared with the computer model. Given the similarities between QUICKI and HOMA, the two methods compare well.

In conditions like diabetes, glucose intolerance, and hyperlipidemia associated with insulin resistance, or with various combinations of these metabolic disorders, QUICKI index values have been observed to be lower when compared to those of healthy volunteers. Adult patients with a QUICKI index below 0.357 (which is at the lower limit of 95% confidence limits in healthy people) tend to have a higher risk or frequently present with typical manifestations of metabolic syndrome[57]. Each laboratory should establish its own normal QUICKI range, since variations in insulin determinations of different laboratories is unavoidable.

Minimal model analysis of the frequently sampled intravenous glucose tolerance test
The minimal model is a method to obtain an indirect measurement of metabolic insulin sensitivity/resistance was developed by Bergman *et al*[58] in 1979. Glucose and insulin values obtained during a FSIVGTT are used in this method.

The data collected by this method, which involves multiple blood sampling, is subjected to minimal model analysis, using the computer program MINMOD to generate an index of insulin sensitivity (IS). After an overnight fast, glucose is infused intravenously over 2 min, starting at time 0. Presently, a modified FSIVGTT is used where exogenous insulin is also infused after the intravenous glucose bolus[59-61] followed by the extraction of blood samples for the estimation of plasma glucose and insulin measurements at -10, -1, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 160, and 180 min.

In contrast to the glucose clamp and IST, which depend on steady-state conditions, the minimal model approach employs the use of dynamic data. Minimal model analysis of the modified FSIVGTT being less demanding in terms of labour, as there are no intravenous infusions and not requirement for steady-state conditions, it is generally found to be easier than the glucose clamp method. The minimal model method[62] is a simple method, but the complexity of the sampling procedure, the sophisticated data analysis, and the correspondingly higher cost make it unsuitable for clinical settings.

Glucose insulin (GI) product
Application of the product of the plasma glucose and insulin concentrations during the OGTT has also been supported by few researchers as an index of whole-body insulin sensitivity[63,64]. IR can be envisaged by increased plasma insulin in spite of normal or increased plasma glucose concentrations. The product of the plasma glucose and insulin concentrations provides the better index of insulin sensitivity. Furthermore, the higher the plasma glucose level, along with a higher plasma insulin response, the more severe is the state of insulin resistance. The lower the GI product, the more responsive are the tissues of the body to insulin. Nonetheless, Matsuda and Defronzo found that this measure correlated well with rate of insulin-mediated glucose disposal during the euglycemic insulin clamp[50].

Fasting insulin resistance index
The fasting insulin resistance index (FIRI) was formulated

Table 2 Various derived surrogate markers of insulin resistance

S No	Method	Measurement	Comments
1	Matsuda index	$10\,000/\sqrt{}$ (fasting G × fasting I) (mean G × mean I)	Represents both hepatic and peripheral tissue sensitivity to insulin.
2	Gutt index	$75\,000 + (G_0 - G_{120})$ (mg/dL) × 0.19 × BW/120 × $Gmean_{(0, 120)}$ (mmol/L) × Log $[Imean_{(0, 120)}]$ (mU/L)	Good to predict onset of type 2 diabetes
3	Stumvoll index	$0.156 - 0.0000459 \times I_{120}$ (pmol/L) $- 0.000321 \times I_0$ (pmol/L) $- 0.00541 \times G_{120}$ (mmol/L)	Utilizes demographic data like age, sex and BMI along with plasma glucose and insulin to predict insulin sensitivity
4	Avignon index	$Sib = 10^8/[I_0$ (mU/L) × G_0 (mmol/L) × VD) $Si2h = 10^8/(I_{120}$ (mU/L) × G_{120} (mmol/L) × VD]	Determines glucose tolerance and insulin sensitivity in single test
5	Oral glucose insulin sensitivity index	G and I concentrations from a 75 g OGTT at 0, 2, and 3 h (3 h OGTT) or at 0, 1.5, and 2 h (2 h OGTT). The formula includes six constants	
6	Log (HOMA-IR)	Evaluates insulin resistance in insulin-resistant states like glucose intolerance and mild to moderate diabetes	

Sib: Derived from fasting plasma insulin and glucose; Si2h: Derived from fasting plasma insulin and glucose ant 2 h of OGTT; OGTT: Oral glucose tolerance test.

by Duncan *et al*[37] in search of a distinct marker, as the use or ratio of glucose and insulin might not be reliable for the estimation of IR. Increased insulin secretion to restore a normal level of plasma glucose leads to persistent elevation of insulin and probably of glucose also.

FIRI is calculated as FIRI = (fasting glucose × fasting insulin)/25.

Derived surrogate markers

Clinical investigators have been in search of more practical indices that measure insulin sensitivity comparable to that of the euglycemic hyperinsulinemic clamp. Such indices of whole-body insulin sensitivity derived from plasma glucose and insulin concentrations during OGTT reflect both muscle and liver insulin sensitivity (see Table 2).

Matsuda index

Several methods have been described that derive an index of insulin sensitivity from the OGTT. In these methods, the ratio of plasma glucose to insulin concentration during the OGTT is used. A novel assessment of insulin sensitivity that is simple to calculate and provides a reasonable approximation of whole-body insulin sensitivity from the OGTT was developed by Matsuda and Defronzo, and is referred to as the Matsuda index[50]. Here the OGTT index of insulin sensitivity [ISI (composite)] was calculated using both the data of the entire 3 h OGTT and the first 2 h of the test.

The composite whole-body insulin sensitivity index (WBISI), developed by Matsuda and DeFronzo is based on insulin values given in microunits per millilitre (μU/mL) and those of glucose, in milligrams per decilitre (mg/dL) obtained from the OGTT and the corresponding fasting values[50].

WBISI= $10\,000/\sqrt{}$ (fasting glucose × fasting insulin) (mean glucose × mean insulin)

This index represents a composite of both hepatic and peripheral tissue sensitivity to insulin.

Gutt index

Gutt *et al*[65] also explored the use of OGTT values in order to try and develop an easy measure of insulin

sensitivity. A formula for an insulin sensitivity index, ISI (0, 120), that used the fasting (0 min) and 120 min post-oral glucose (OGTT) insulin(I) and glucose(G) concentrations along with body weight (BW) was devised.

$ISI_{(0, 120)}$ = $75\,000 + (G_0 - G_{120})$ × 0.19 × BW/120 × $Gmean_{(0, 120)}$ × Log $[Imean_{(0, 120)}]$ Insulin concentration is expressed in mU/L and glucose concentration is expressed as mg/dL in the numerator and mmol/L in the denominator. It was shown to correlate well with the insulin sensitivity index obtained from the euglycemic hyperinsulinemic clamp.

Stumvoll index

It is now possible to calculate insulin sensitivity and insulin release from simple demographic parameters and values obtained during an OGTT with practical precision.

Stumvoll *et al*[66] proposed use of demographic data like age, sex and basal metabolic rate (BMI) in addition to plasma glucose (mmol/L) and insulin (pmol/L) responses during the OGTT to predict insulin sensitivity and beta cell function.

$ISI_{Stumvoll}$ = $0.156 - 0.0000459 \times I_{120} - 0.000321 \times I_0 - 0.00541 \times G_{120}$

$ISI_{Stumvoll}$ = $0.222 - 0.00333 \times BMI - 0.0000779 \times I_{120} - 0.000422 \times Age$

The metabolic clearance rate of glucose and ISI calculated by this method included BMI, insulin (120 min), and glucose (90 min).

These parameters correlated better with the measured parameters than the homeostasis model assessment for secretion and resistance[66].

Avignon index

Avignon *et al*[67] tried to compare IS indicesindices which were derived from plasma insulin (I) (mU/L), glucose (G) (mmol/L) and apparent glucose distribution volume in the basal state (Sib), and at the end of second hour OGTT (Si2h). Another insulin sensitivity index (SiM) was calculated by averaging Sib and Si2h.

Table 3	Imminent markers of insulin resistance
S No	**Marker**
1	Insulin growth factor binding protein-1 (IGFBP-1)
2	sCD36 (solubleCD36)
3	C-reactive protein (CRP)
4	Ferritin
5	Adiponectin
6	Tumour necrosis factor (TNF alpha)
7	Resistin
8	C3 complement
9	Glycosylated hemoglobin (Hb)A1c
10	Protein kinase C (PKC) in microangiopathy
11	Sex hormone-binding globulin (SHBG) in hyperandrogenic syndrome

$SiM = [(0.137 \times Sib) + Si2h]/2$, where $Sib = 10^8/(I_0 \times G_0 \times VD)$ and $Si2h = 10^8/(I_{120} \times G_{120} \times VD)$ (VD is an estimate of the apparent glucose distribution volume).

It was observed that the results obtained by computation of sensitivity indicesindices from G and I concentrations in the basal state and during a conventional 2 h OGTT were useful for blending both a determination of glucose tolerance and an estimate of insulin sensitivity in a single and simple test.

Oral glucose insulin sensitivity index

Another group of researchers developed an index of insulin sensitivity which was calculated using a model-derived principle from the OGTT glucose and insulin concentration. This index was found to be equivalent to glucose clearance calculated during a clamp[68].

The oral glucose insulin sensitivity index requires glucose and insulin concentrations from a 75 g OGTT at 0, 2, and 3 h (3 h OGTT) or at 0, 1.5, and 2 h (2 h OGTT). The formula includes six constants optimized to match the clamp results. This is validated against the clamp method in subjects with IGT and type 2 diabetes.

Log (HOMA-IR)

Log (HOMA-IR) is useful for the assessment of insulin resistance in insulin-resistant conditions like glucose intolerance and mild to moderate diabetes. In research studies where assessing insulin sensitivity/resistance is of secondary interest, it may be appropriate to use log (HOMA-IR) instead of the direct use of HOMA.

In the case of relentlessly deranged/β-cell function, HOMA-IR may not give an apposite method to evaluate IR. The coefficient of variation for HOMA-IR varies greatly, depending upon the number of fasting samples obtained and the type of insulin assay used[50,51,69,70]. Log (HOMA-IR) transforms the skewed distribution of fasting insulin values to determine a much stronger linear correlation with glucose clamp estimates of insulin sensitivity when extensive ranges of insulin sensitivity/resistance are being studied[37].

Log (HOMA) is being applied broadly in large epidemiological studies, and in clinical research studies[51,52,71].

Imminent markers

With the passing of time and ongoing intensified research, many newer particles are gaining attention as surrogate markers in assessment of IR. In recent times, inflammatory markers have gained popularity in terms of assessment of insulin resistance (Table 3).

Insulin growth factor binding protein-1

Current research has recommended insulin growth factor binding protein-1 (IGFBP-1) as a new potential plasma marker to assess insulin resistance[72]. IGFBP-1 has been found to have a good correlation with FSIVGTT assessment of insulin sensitivity, mainly in children younger than 10 years[72]. However, more studies are required to authenticate the usefulness of this marker. IGFBP-1 levels decline with obesity and IR. Although elevated fasting insulin is less sensitive but more specific, it has been suggested that in young subjects, IGFBP-1 might act as a convenient and susceptible marker of IR. It is an emerging marker which may be useful in this context.

SolubleCD36

Macrophage CD36 is a key proatherogenic molecule that scavenges oxidized low-density lipoprotein, leading to foam cell formation. Hyperglycemia and altered macrophage insulin signaling in insulin resistance leads to increased expression of CD36[73]. SolubleCD36 has been reported to be distinctly elevated in patients with type 2 diabetes and insulin resistance[73].

It is postulated that it might represent a potential marker of IR and its complications.

C-reactive protein

C-reactive protein (CRP) is one of the best studied markers for systemic subclinical inflammation, and may have prognostic value in predicting the future risk of cardiovascular events[74]. In cross-sectional studies, highly sensitive - CRP has been found to correlate with increased triglyceride, decreased HDL, increased blood pressure and increased fasting plasma glucose concentrations, suggesting its association with increased prevalence metabolic syndrome associated with IR[75,76]. Few studies have established the association of CRP with IR independent of obesity[77].

In a recent study, CRP was found to significantly associate with several surrogate measures of IR like fasting insulin, the Raynaud index, the quantitative insulin sensitivity check index, and the McAuley index, HOMA, QUICKI, the Insulin: glucose ratio and the Avignon index in non-diabetics[78]. Because of the simplicity of measurement, stability, and improved high-sensitivity method, CRP may be useful as a clinical measure for identifying individuals at risk for IR[79].

Ferritin

Ferritin is the major intracellular iron storage protein. Recently it has been suggested that when markers of the iron metabolism are elevated, the incidence of the metabolic syndrome is increased[80]. Ferritin has been associated with

both hyperinsulinemia and hypertriglyceridemia. Metabolic disorders are common among patients with high ferritin without genetic hemochromatosis, than among patients with genetic hemochromatosis. Iron deposition in various tissues affects insulin sensitivity and function, thereby leading to insulin resistance and inflammation.

A few studies have demonstrated a link between markers of insulin resistance (HOMA-IR, fasting insulin) and ferritin[81]. Fumeron *et al*[82] also found that plasma ferritin concentrations positively correlate with fasting insulin and fasting glucose.

Adiponectin

Adiponectin is a multifunctional protein that exerts pleiotropic insulin-sensitizing effects and hence is considered as a key molecule in the pathogenesis of metabolic syndrome[83,84]. It lowers hepatic glucose production[85] and increases glucose uptake and fatty acid oxidation in skeletal muscle[86]. Adiponectin levels are decreased in obesity and are inversely correlated to insulin-resistant states and high-sensitivity CRP levels[87].

Deranged levels of adiponectin have been found to be related to insulin resistance. Adiponectin appears to have a stronger negative correlation with HOMA in individuals without the metabolic syndrome as compared to those with metabolic syndrome[88].

Several prospective studies have confirmed that hypoadiponectinemia was associated with an increase in insulin resistance[89] and an elevated risk of developing diabetes[90,91].

Tumour necrosis factor alpha

Several studies have been conducted to explore the role and use of tumour necrosis factor (TNF) to aid in assessing the IR. TNF has been proven to have a relation to insulin resistance measured by HOMA-IR[92] or insulin clamp[93,94] and to metabolic syndrome status[95].

Resistin

The association between resistin and insulin resistance in humans has not been fully established. Many studies have been unsuccessful in recognizing an association between resistin and measures of insulin resistance[96,97]. On the other hand, a few studies have been conducted which have indeed discovered a significant relationship between IR (HOMA-IR) and resistin[88,98-100].

C3 complement

The main activation fragment of C3, C3a desArg (acylation stimulating protein) favours glucose transmembrane transport and the synthesis of triglycerides in adipocytes. This suggests that it has insulin-like properties[101]. C3 is strongly linked with insulin resistance (as defined according to the homeostasis model assessment (HOMA), independent of the components of the metabolic syndrome[102]. The strong association of C3 with insulin action and fasting insulin has been reported in young adult Pima Indians[103].

Glycosylated hemoglobin

Glycosylated hemoglobin (HbA1c) has been used to review long-term glycemic control in diabetics. However, its role and clinical worth in patients suffering from IR or metabolic syndrome in nondiabetic subjects is dubious. HbA1c has been proposed as a measure of surrogate assessment of metabolic syndrome, thereby estimating IR because of various factors. HbA1c reflects long-term glycemic control in diabetic patients and is a significant predictor of long-term complications of diabetes[104,105]. Though HbA1c cannot be considered as a screening or diagnostic tool for diabetes, it has been demonstrated that HbA1c represents both fasting and postprandial glycemic states[106-111].

Upper normal levels of HbA1c in the range of 5.7%-6.4% have been found to echo some components of insulin resistance syndrome or metabolic syndrome[112]. A study conducted in the nondiabetic, obese, first-degree relatives of African-Americans who were genetically predisposed to type 2 diabetes[112] showed significantly high HOMA IR, reduced insulin sensitivity and reduced glucose effectiveness in the nondiabetic study group. Insulin sensitivity and glucose effectiveness were calculated using Bergman's Minmod software program[113,114].

It has been postulated that HbA1c can be considered predictive of insulin resistance.

Protein kinase C in microangiopathy

It has been speculated that activation of the protein kinase C b isoform (PKCb) which is mediated by hyperglycemia acts as a potential surrogate marker for microangiopathic diseases, and diabetic retinopathy in particular[115]. A study conducted on diabetic patients correlated PKC activation with diabetic retinopathy. It was suggested that PKC activation in mononuclear cells may serve as a surrogate marker for diabetic microangiopathy[115].

Sex hormone-binding globulin in hyperandrogenic syndrome

Sex hormone-binding globulin (SHBG) may serve as a predictive marker of IR in obese women suffering from hyperandrogenic syndrome. In a study conducted by Kajaia *et al*[116], IR was established by means of the Matsuda ISI in hyperandrogenic women, who were discovered to have significantly lower SHBG and HDL levels. SHBG may be regarded as an extrapolative marker in these types of cases.

CONCLUSION

To summarize, this article is an attempt to scrutinize a variety of methods currently available for estimating insulin sensitivity/resistance. Assessment of insulin resistance is increasingly being exploited in clinical situations, and this calls for the existence of relatively simple markers. The application of surrogate markers is a useful tool with which to gauge IR. These vary from intricate, time-consuming and invasive procedures, to simple tests

involving a single fasting blood sample. The glucose clamp method has been the reference standard for direct measurement of insulin sensitivity. With regard to simple markers, HOMA and QUICKI are among the best and most extensively validated surrogates that can give a more physiological estimate of glucose homeostasis. Other derived indirect indices have been recognised that correlate well with those derived from clamp studies. It is important to understand the concepts and relative merits and limitations underlying each method in order to correctly interpret the data for measuring insulin sensitivity. Several novel markers like the insulin growth factor binding protein-1, hs-CRP, adiponectin, ferritin, HbA1c, C3 complement, TNF alpha and sCD36 are now surfacing as surrogate markers of IR.

The use of surrogate markers to assess insulin resistance might thus help to use medical resources to fullest, while minimizing costs and inconvenient side effects.

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