A Brief Review of Commonly Used Indices for the Assessment of Insulin Sensitivity and Resistance

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Abstract

Insulin resistance (IR) results when the response to the physiological actions of insulin is reduced. Approximately, 45% of adults around the world have some degree of IR. This reduced responsiveness to insulin action leads to a variety of clinical conditions like metabolic syndrome which includes a group of deranged clinical and biochemical profile including increased body weight, elevated blood pressure, an abnormal lipid panel, and intolerance to glucose.

The hyperinsulinemic euglycemic clamp (HEC) remains the gold standard technique but it is cumbersome, costly, time consuming, and liable for operator errors. Hence, different indices assessing insulin sensitivity were introduced. Some of these indices can, in part, be calculated utilizing fasting levels of insulin and glucose whereas others are calculated following performing metabolically provocative tests like the oral glucose tolerance test (OGTT). This article will review different techniques and parameters that are currently being used for the assessment if insulin sensitivity and resistance.

Introduction:

Insulin resistance (IR) is the situation that results when the tissue response to the physiological actions of insulin is reduced [1]. It is estimated that about up to 45% of adults around the world have some degree of IR [2]. This reduced responsiveness to insulin action leads to a variety of clinical conditions like diabetes mellitus increased cardiovascular risks, but metabolic syndrome...
may be the most notorious one of them. The metabolic syndrome that develops in subjects with IR includes a group of deranged clinical and biochemical profile including increased body weight, elevated blood pressure, an abnormal lipid panel, and intolerance to glucose [3].

Despite the versatile techniques used for estimating the sensitivity to insulin actions and its rate of production, yet the hyperinsulinemic euglycemic clamp (HEC) remains the gold standard technique [4]. The vast majority of insulin sensitivity indices are validated with respect to the HC and HEC techniques. Despite the validity and reproducibility of the aforementioned techniques, nevertheless, they remain cumbersome, costly, time consuming, and liable for operator errors making them non practical to be used in everyday routine clinical practice or in large-scale clinical trials. Hence, the need for a different measure to replace the clamp techniques, for assessing the secretion rate of insulin and peripheral tissue utilization of glucose in response to insulin, were introduced. These proposed indices and protocols estimate insulin resistance or sensitivity relaying on variables that reflect such a need like serum “insulin” or its equimolar counterpart the “C-peptide”, blood glucose level, or even triglycerides and fatty acids. Fatty acids and triglycerides are coupled with the sensitivity for insulin owing to the fact that insulin plays a pivotal role in their release by its effect on the process of lipolysis [5].

The indices of IR or insulin sensitivity (IS) can, in part, be calculated utilizing fasting levels of insulin and glucose whereas others are calculated following performing metabolically provocative tests like the oral glucose tolerance test (OGTT) [6]. The former set of indices represents a static state of insulin release or more accurately “basal insulin activity” while the latter set represents the dynamic interaction of insulin with glucose or non-esterified fatty acids. The static tests reflect the hepatic gluconeogenesis, i.e., hepatic insulin sensitivity, and the dynamic test reflects the same glucose source in addition to the disposal of glucose from circulation into muscular and adipose tissues, i.e., peripheral tissue sensitivity to insulin [7]. Indices of insulin sensitivity/resistance can also be combined with other markers, like D-dimer or CRP, to evaluate the progression of various diseases in diabetic patients [8].

This article will review different techniques and parameters that are currently being used for the assessment if insulin sensitivity and resistance. These different methods and their derived indices vary from being easy, affordable, and valid for clinical practice to being complex, costly, consuming time and effort. The article will try to cast a light on the simple physiological base behind these methods’ calculation together with advantages and disadvantages of them.

**Common indices of insulin sensitivity (IS)/Insulin resistance (IR)**
Indices of insulin sensitivity can be broadly divided into: (1) direct indices calculated from fasting insulin, fasting glucose, and fasting triglycerides, (2) surrogate indices calculated from plasma insulin and glucose after dynamic tests like OGTT [9].

**Fasting methods for assessing insulin sensitivity:**
These methods have the merit of being easy to perform, uncostly, less vulnerable to human error, and require only one blood sample to be withdrawn after a proper period of fasting. Unfortunately, the drawback is that such methods postulate a linear glucose-insulin relationship when actually it is a parabolic interaction. After fasting for 8-12 hours, a blood sample is withdrawn to measure the fasting serum level of glucose, insulin, and free fatty acids (FFA). From these, the following indices are calculated:
**Fasting serum insulin:**
It is an easy and cost-effective parameter that requires no additional arithmetic formulation. This parameter shows little variability among other indices of the same category. At normal conditions, a fasting serum insulin should be between 5-15 µU/mL, but a fasting serum level of insulin higher than 30 µU/mL strongly suggests resistance to insulin since such a value of insulin would be sufficient to suppress glucose levels in those with an intact beta cell mass and hence there would be euglycemia rather than hyperglycemia [10]. The problem with fasting serum insulin that limits its use as a marker of IR is that it has poor reproducibility and lacks standardization [11].

**Fasting glucose/insulin ratio (FGIR):**
This ratio is feasible, easy to calculate and has good sensitivity to insulin resistance. In healthy situation, the continuous insulin-glucose interaction keeps both parties within their reference values. In conditions where insulin is found in higher-than-normal levels yet the subject is relatively euglycemic, the ratio decreases and IR is highly suspected with the risk for progressing into frank diabetes is being significant [12]. A value of <4.5 is suggestive of insulin resistance especially in females with polycystic ovarian syndrome [13].

**Homeostasis model assessment of insulin resistance (HOMA-IR):**
HOMA-IR is calculated using the following equation [14]:

\[
HOMA-IR = \frac{\text{fasting insulin (µU/L)} \times \text{fasting glucose (nmol/L)}}{22.5}
\]

\[
HOMA-IR = \frac{\text{fasting insulin (µU/mL)} \times \text{fasting glucose (mg/dL)}}{405}
\]

HOMA-IR has established itself as a powerful marker of IR but it lacks a clear cut-off point and shows high variability among different populations. A HOMA-IR value of > 2 in adults indicates insulin resistance [14, 15].

**Homeostasis Model Assessment of Beta-cell function (HOMA-%B):**
The HOMA-%B is similar to HOMA-IR where it needs only a fasting blood sample to be calculated according to the following formulae [16]:

\[
HOMA-%B = \frac{20 \times \text{fasting insulin (µU/ml)}}{[\text{fasting plasma glucose (mg/dL)} - 63]}
\]

\[
HOMA-%B = \frac{20 \times \text{fasting insulin (µU/ml)}}{[\text{fasting plasma glucose (nmol/L)} - 3.5]}
\]

Since HOMA-%B is directly proportional to fasting level of insulin, it is expected to reveal a direct relation to insulin resistance in those who are glucose tolerant [16].

**Quantitative insulin sensitivity check index (QUICKI index):**
is relatively similar to HOMA-IR by utilizing a single fasting blood sample. The QUICKI index is calculated according to the following equation [17]:

\[
QUICKI = \log \left[ \frac{1}{\text{fasting insulin (µU/mL)} \times \text{fasting glucose (mg/dL)}} \right]
\]

This logarithmic relationship increases the accuracy of QUICK index in comparison to HOMA in calculations covering a wider range of insulin and glucose fluctuations. The reference value of
QUICKI is 0.38 ± 0.007 for lean people, 0.33 ± 0.010 for overweight people, and 0.30 ± 0.007 for those with diabetes [18].

Adipose Tissue Insulin Resistance Index (Adipo-IR):
From the physiological point of view, the adipo-IR is similar to HOMA-IR by being calculated from the fasting insulin and the fasting free fatty acids (FFA) according to the following equation [19]:

$$Adipo-IR = \left( \frac{\text{mmol} \times \text{pmol}}{L} \right) \times \left[ \frac{\text{Fasting FFA (mmol/L)}}{\text{Fasting insulin (pmol/L)}} \right]$$

There are several factors that affect adipo-IR including the age and the fitness of the subject from the physical point of view. Therefore, this parameter may be handy in studies involving large population size [20].

McAuley index (MACi):
This index has the capability of predicting insulin resistance in those with normoglycemia. McAuley index correlates triglyceride levels to fasting insulin upon predicting insulin resistance according to the following equation [21]:

$$\text{MACi} = \exp \left( 2.63 - 0.28 \ln(FI_{(mIU/l)}) - 0.31 \ln(TG_{(mmol/l)}) \right)$$

An increasing value of MACi signifies an increased level of IR. Upon comparison of McAuley's index with other IR indices, it showed greater accuracy, higher positive predictive values, and higher sensitivity [22].

B. Surrogate indices calculated after dynamic tests:
These indices are calculated after performing dynamic test that takes into account the second-to-second variability of glucose-insulin interaction. Since the pathophysiology behind IR is multifaceted involving abnormal secretion of insulin or abnormal response to the hormone, these surrogates are more useful in exploring the cause of IR [23]. Such indices and methods include the following:

Oral Glucose Tolerance Test (OGTT) and its derived indices:
This test has the virtue of being closer than the other test to the insulin-glucose interaction from the physiological point of view. The OGTT is widely used in clinical practice to screen for insulin resistance [24]. The patient fast for an overnight after which he/she is given a standard oral dose of a 75 mg glucose in a glass of water. The patient remains seated throughout the test and blood samples are withdrawn at half hourly intervals for 2 hours beside that taken at time zero (i.e., the start of test). This test measures the ability of the body to clear glucose after an oral load. An important point is needed to be emphasized, that the OGTT reflects the tolerance to glucose rather than insulin resistance since there are many intervening factors that affect the test results like the effect of incretin. From the OGTT, several indices can be derived to estimate insulin sensitivity/resistance [25].

Hyperinsulinemnic euglycemic clamp technique:
This technique is regarded as the gold standard procedure that is resorted to whenever the validity of other indices or techniques are apt to be validated. In principle, this technique depends on achieving a steady-state of blood insulin level that is slightly above the basal reference point (i.e., a steady hyperinsulinemia) and to maintain the blood glucose level within the reference range (i.e., steady euglycemia) [26]. This is done by a continuous and simultaneous infusion of calculated
dose of both, insulin and glucose. At this steady insulin-glucose state, the hyperinsulinemia would be sufficient to suppress hepatic gluconeogenesis and hence preventing adding up glucose into circulation. Therefore, at this point, the clearance of glucose from circulation is mainly due to uptake and metabolism in skeletal myocytes and adipocytes of the white adipose tissue [15]. Additionally, at this steady-state, the rate at which glucose being infused is equal to the rate at which glucose being cleared by metabolism (\(M_{\text{glucose}}\)) and hence the latter can be calculated with ease and be incorporated into equating in order to calculate an index of insulin sensitivity index known insulin sensitivity index from clamp technique (SI\text{clamp}) which is calculated as follows [4]:

\[
IS_{\text{clamp}} = \frac{M}{G \times \Delta I}
\]

Where, \(M\) = glucose disposal (clearance) rate, \(G\) = the glucose concentration at the steady state, and \(\Delta I\) is the difference in insulin concentration from the start of the test up to the steady state point. The disadvantage of HEC is that it is being costly, time-consuming, and operator dependent [27].

**Insulin suppression test (IST):**
In this test, the subject fasts for 10-12 hours and the body endogenous insulin secretion is completely suppressed beside glucagon using either intravenous infusion of a calculated dose of somatostatin or its analogue, octreotide [28]. At the same time, exogenous insulin together with glucose are continuously infused until reaching a steady state of insulin-glucose interaction, commonly after 3 hours of the test. Once the steady state has been reached, blood samples are withdrawn at different intervals to determine the level of both insulin and glucose [29]. At this point, if the test subject was having some sort of insulin resistance, he/she would have higher than reference values of insulin since under such a condition, more than the usual insulin is required to maintain glucose homeostasis. The IST has the advantage of being less time consuming and easier to perform in comparison to HEC and therefore can be used for studies based on large population scale [30].

**Frequently sampled intravenous glucose tolerance test (FSIVGTT):**
like the aforementioned tests, the test subjects fast for an overnight and is given, over a period of 2-minutes, an infusion of a bolus dose of glucose calculated based on body weight. After glucose infusion, frequent blood samples are withdrawn at intervals for up to a total test duration of 180 minutes [31]. From these samples, the basal insulin (before starting the test) together with blood levels of insulin and glucose at different test intervals are all calculated. These data collected after FSIVGTT are the processed in a designated computer software called MINMOD to be subjected for minimal model analysis. After data processing, the following indices will be yielded [32]:

- Sg index is the capability of glucose to inhibit hepatic gluconeogenesis without the need for an increasing dose of insulin (i.e., at basal insulin levels) and at the same time its ability to stimulate its own clearance [33].
- Si index which is clearance of glucose from circulation in response to variable increments of insulin [33].

**Belfiore index:**
The Belfiore index is calculated from glucose and insulin values during OGTT. This index mainly depends upon comparing the results of glucose and insulin at zero time of OGTT and the results
obtained after the first and second hours of the test, comparing them with predefined reference values of normal subjects [34]. Belfiore index is calculated as follows:

\[
\text{Belfiore index} = \frac{2}{(I_S) \times (G_S)} \times 1
\]

The subscripts S stands for (subject being tested) and the N stands for (reference values of normal subjects). The results of Belfiore index range eventually from 0-2. Normal and lean person will have a value close to 1, in case of obesity, diabetics of type 2, and impaired glucose tolerance, the index would be <1 [35].

**Matsuda index:**
This index is measured from the insulin (in µU/L) and glucose concentrations (in mg/dL) during OGTT according to the following formula [36]:

\[
\text{Matsuda index} = \frac{1000}{\sqrt{\text{Fasting insulin} \times \text{Fasting glucose} \times (\text{mean glucose} \times \text{mean insulin})}}
\]

The Matsuda index is simple to calculate and shows good estimation for insulin sensitivity.

**Cederholm index:**
This parameter reflects the sensitivity of the peripheral tissues to insulin and the mobilization rate of glucose into the muscular tissue since both of these glucose utilizing tissues are the key players in insulin clearance after OGTT [37].

**Stumvoll index:**
This index incorporates additional parameters beside blood glucose and insulin gained during OGTT like the body weight, represented by the body mass index (BMI), gender, and age and hence might be preferable in epidemiological researches. The problem with is that it correlates weakly in diabetics [38]. The Stumvoll index is calculated as follows:

\[
\text{Stumvoll index} = 1194 + 4.724 \times [\text{Insulin}]_{\text{at time zero}} - 117.0 \times [\text{Glucose}]_{\text{at time 60}} + 1.414 \times [\text{Insulin}]_{\text{at time 60}}
\]

**Avignon index:**
This index involves three IS indices: Sib (calculated using fasting insulin and glucose levels), Si2h (calculated using insulin and glucose levels after two hours of OGTT) and SiM (calculated by multiplying Sib by 0.137 and then taking the average of Sib and Si2h combined [39, 40].

**Conclusion:**
Screening for insulin resistance should be incorporated in routine clinical practice owing to the fact that it is a hidden risk factor for a variety of adverse clinical outcomes. Hence, the proper selection of the tool or the technique for such screening is highly important. The hyperinsulinemic euglycemic clamp method remains the standard techniques to directly assess insulin resistance but it is not suitable for everyday clinical practice. The simpler forms of IS indices such as QUICKI, HOMA indices, and Matsuda index remain better candidates to screen for insulin sensitivity/resistance due to their ease, validity, and reproducibility.

**Conflict of interests:**
non to be declared.
References