Abstract

Insulin resistance represents a major public health problem, as it plays a major role in the pathophysiology of type 2 diabetes mellitus; it is also associated with increased cardiovascular risk and atherogenic dyslipidaemia, and is a central component of the cluster of metabolic abnormalities that comprise the metabolic syndrome. Thus, the development of tools to quantify insulin sensitivity/resistance has been the main objective of a number of studies. Insulin resistance can be estimated with the use of several biological measurements that evaluate different aspects of this complex situation. To that end, it requires various resources, ranging from just a single fasting blood sample for simple indices, such as the HOMA or QUICKI, to a research setting in which to perform the gold-standard hyperinsulinaemic–euglycaemic clamp test. The choice of method for evaluating insulin resistance depends on the nature of the information required (classification of individual subjects, group comparisons, precise measurement of either global, muscle or liver insulin sensitivity/resistance) and on the available resources. The aim of this review is to analyze the most frequently used assay methods in an attempt to evaluate when and why these methods may be useful.

Keywords: Hyperinsulinaemic–euglycaemic glucose clamp; Insulin sensitivity; Insulin resistance; HOMA; QUICKI; OGTT; Review

Résumé

Comment mesurer la sensibilité/résistance à l’insuline?.

La résistance à l’insuline représente un problème majeur de santé publique puisqu’elle joue un rôle central dans la physiopathologie du diabète de type 2, est associée à une augmentation du risque cardiovasculaire et est un élément central d’un ensemble d’anomalies métaboliques qui définissent le syndrome métabolique. Ainsi, de nombreuses études se sont attachées à développer des outils pour apprécier et quantifier la sensibilité/résistance à l’insuline. L’insulino-résistance peut être mesurée de plusieurs façons qui permettent d’en appréhender différents aspects et qui font appel à des méthodes qui vont du simple prélèvement sanguin à jeun, qui permet le calcul des index simples HOMA ou QUICKI, à la méthode de référence du clamp hyperinsulinémique euglycémique. Le choix de la méthode pour évaluer le niveau de résistance à l’hormone dépend de la nature des
informations requises (procéder à un classement de sujets, de groupes, mesurer précisément la sensibilité/résistance à l’insuline globale, musculaire ou hépatique) et des outils disponibles. Le but de cette revue est d’analyser les méthodes le plus fréquemment utilisées afin de clarifier quand et dans quelles situations, elles sont utiles.

1. Introduction

Insulin is a peptide hormone that exerts a variety of effects, mostly anabolic, on different cell types, but mainly in hepatocytes, myocytes and adipocytes. The hormone stimulates cell growth and differentiation, and promotes the storage of substrates in fat, liver and muscle by stimulating lipogenesis and lipid storage, and glycogen and protein synthesis, while inhibiting lipolysis, glycogenolysis and protein breakdown. Thus, resistance to the hormone leads to hyperglycaemia and hyperlipidaemia, while a lack of insulin results in protein-wasting, ketoadipospermia and, ultimately, death [1]. Although insulin is central to all intermediary metabolic processes, its main action is related to glucose homoeostasis. Therefore, insulin resistance is typically defined as a decrease of insulin-mediated glucose disposal in insulin-sensitive tissues and increased hepatic glucose production (HGP). Peripheral insulin resistance—in other words, reduced insulin sensitivity—refers to a low capacity to utilize glucose in target tissues, mainly skeletal muscle, where it affects glucose transport and glycogen synthesis. At the level of adipose tissue, the main feature of insulin resistance is increased lipolysis via decreased antilipolytic insulin activity [2,3]. In addition, hepatic insulin resistance refers to increased glucose production by the liver via impaired inhibition of glycogenolysis and stimulation of gluconeogenesis [3,4]. Overall, insulin is implicated in numerous cellular mechanisms and in key tissues, such as muscle, in which insulin regulates over 700 genes [5].

Since the definition of the metabolic syndrome in the 1980s by Reaven [6], who first proposed that insulin resistance was clustered together with numerous cardiometabolic abnormalities (hyperglycaemia, elevated plasma triglycerides [TG], low levels of high-density lipoprotein [HDL] cholesterol and hypertension) in association with the emergence of the obesity pandemic, insulin resistance has gained in importance. Insulin resistance is a major component of several significant cardiometabolic abnormalities, including the metabolic syndrome, type 2 diabetes and cardiovascular disease (CVD) [7]. Their presence strongly suggests evidence of an insulin-resistant state, but does not either demonstrate its presence or quantify it. Some nonobese subjects may present with all of the metabolic abnormalities, whereas other obese subjects may not present with any metabolic abnormality and be classified as metabolically normal [8,9]. Moreover, insulin resistance is not always pathological, and may be observed in physiological states such as pregnancy and puberty [10]. In addition, there is considerable overlap of the insulin sensitivity/resistance distribution between the physiological and pathological states [10]. Thus, the development of tools to quantify insulin sensitivity/resistance has been the main focus of several studies. Such studies can provide information on the underlying pathophysiological mechanisms, and may be associated with clinical and therapeutic outcomes in the field of diabetes and CVD.

The different methods available for measuring insulin sensitivity/resistance have been exhaustively reviewed elsewhere [11–18]. For this reason, the aim of the present review is to discuss the most frequently used tests in clinical research and to focus on the surrogate methods currently available.

1.1. The importance of insulin assay

In addition to most dynamic tests to evaluate insulin resistance, all the simple surrogate indices for insulin sensitivity/resistance estimation mainly depend on insulin values. These are particularly important in the fasting state, when insulin levels are relatively low and a small difference in its measurement could considerably impact the surrogate indices. Also, it is important to consider that the insulin assay itself might be critical at both the preanalytical and analytical levels. In addition to the well-known importance of avoiding haemolyzed samples for insulin assay, it is important to note that insulin levels are higher in serum than in plasma samples, with differences that are proportional to insulin concentrations [19]. Therefore, even while using the same analytical procedures, when insulin values are derived from both serum and plasma samples in a study, they cannot be compared.

Furthermore, it is not possible to compare the results of surrogate indices where different insulin assays have been used, as may be the case in multicentre studies where insulin has not been centrally tested. Indeed, a twofold difference in insulin values has been reported in a study investigating 11 different types of human insulin assays [19]. Standardization of these insulin assays may thus improve several variations that preclude such comparisons between studies [20]. Recently, the Insulin Standardization Work Group recommended that concentrations of insulin be reported in international units (SI, pmol/L), thereby avoiding all references to traditional insulin units based on insulin biological activity per milligram of standard preparation [20,21].

On the other hand, the Work Group also showed that most commercial insulin assays [21] can achieve consistent performance with calibration traceability based on individual serum samples, with insulin concentrations set by isotope dilution–liquid chromatography/tandem mass spectrometry measurement, a procedure that is calibrated using purified recombinant insulin. They also observed that several, but not all, insulin assays were acceptable for precision, accuracy and cross-reactivity. However, performance of these insulin assays was not similar at low concentrations, a critical point when determin-
ing cut-off values between normal and insulin-resistant states. Therefore, a serious and sustainable insulin assay standardization programme needs to be established [20], as this will likely improve the reliability of surrogate indices of insulin sensitivity.

2. Frequently used exploration tests in clinical research

2.1. Hyperinsulinaemic–euglycaemic glucose clamp

The hyperinsulinaemic–euglycaemic glucose (HIEG) clamp test is accepted as the gold standard procedure for the assessment of insulin sensitivity in clinical research. The procedure, as described by DeFronzo et al. [22], consists of both a constant intravenous infusion of insulin to create an artificially constant hyperinsulinaemic state and a variable glucose infusion to maintain a euglycaemic state. For this procedure, intravenous catheterization of one arm is necessary throughout the test for both the glucose and insulin infusions. During the test, arterial oxygenated blood glucose difference increases in proportion to the rate of insulin infusion and insulin sensitivity. Thus, adjusting glucose infusion rates (GIR) from venous glycaemia may lead to overestimation of insulin sensitivity.

To avoid such a drawback, arterial catheterization—or, at least, arterialized blood—may be obtained via retrograde cannulation of a wrist vein warmed with a heating pad. This allows the opening up of arteriovenous anastomoses as is required for blood glucose measurement. However, in one comparative study, Nauck et al. [23] showed that HIEG clamp experiments using venous, arterialized venous and capillary euglycaemia were all nearly equally useful for determination of insulin sensitivity. Glucose levels were maintained (at 80–90 mg/dL or 4.45–5.00 mmol/L) by monitoring the glucose level every 5 or 10 min, and adjusting the infusion rate of a 20% dextrose solution. The constant insulin infusion produces a new steady state, with a plateau of insulin concentration sufficiently above fasting levels to suppress HGP, and to increase glucose disposal in skeletal muscle and adipose tissue.

Under such a state of constant glycaemia, the GIR equals the glucose disposal rate (M), which is the mean rate of glucose infused in the last 30 min of the clamp test, which overall lasts around 2 to 3 h. Thus, we can calculate the glucose disposal per unit of plasma insulin concentration in a steady state (M/I). Usually, M is expressed in mg/kg body weight/min. However, as most of the glucose uptake occurs in muscles and only a small proportion in adipose tissue, the GIR expressed as M (in mg/kg/min) could overestimate insulin resistance in obese subjects [11]. For this reason, it has been proposed to normalize M to fat-free mass (FFM) (mg/kg_{FFM}/min) or to lean body mass (mg/kg_{LBM}/min), which should be more representative of insulin sensitivity whatever the subject’s body mass index (BMI).

However, this concept was recently criticized, as it was shown that adipose tissue contributes notably to insulin-mediated glucose uptake in morbidly obese subjects [24]. Thus, it has been proposed that the M value should be normalized by kg body weight instead of FFM in such subjects [24]. Nevertheless, when normalization by FFM is required, body composition measurement can be done by relatively simple measures such as bioimpedance or the more precise dual X-ray absorptiometry (DXA). Furthermore, the results can also be expressed as $SIC_{\text{clamp}} = M/(G \times \Delta I)$, where G is the steady-state plasma glucose (SSPG) level, and $\Delta I$ the difference between fasting and steady-state plasma insulin levels [17].

The validity of HIEG clamp measurements depends on the complete suppression of HGP by insulin. In cases where HGP is not suppressed, M underestimates the total amount of glucose metabolized. Suppression of HGP is achieved with an insulin infusion rate of 40–60 mU/m²/min (dose/body surface area/time) in nonobese (BMI < 25 kg/m²) nondiabetic subjects in most, but not all, cases [22]. In some situations (overweight, obesity or type 2 diabetes) where HGP is not totally inhibited by such an infusion rate, HGP can be measured using an infusion of glucose labelled with stable isotopes and/or a higher rate of insulin infusion ($\geq 80$ mU/m²/min) to ensure a high probability of HGP suppression [16].

The use of different insulin rates during the HIEG clamp, producing different steady-state levels, allows determination of the dose–response curves between increasing insulin concentrations and increases in glucose disposal rate. In this way, Rizza et al. [25] found that the maximum effect of insulin in control subjects occurred at insulin concentrations of 200–700 µU/mL, while the half-maximum effect was seen at 42–89 µU/mL, a level that can be obtained with an insulin infusion rate of 40 mU/m²/min or 1 mU/kg/min.

The HIEG clamp test requires that glycaemia be clamped at a predetermined value in the normal range. This is easily achieved in normoglycaemic subjects, but is more complex in diabetic patients because of the variability of previous plasma glucose levels. When plasma glucose is high after an overnight fast in diabetic patients, intravenous insulin should be given to normalize plasma glucose before starting the clamp. However, this procedure, which may require some time to achieve, may induce acute changes of glycaemia and, thus, alter insulin sensitivity. Therefore, some investigators prefer clamping plasma glucose at its fasting level (isoglycaemia). However, in this case, it is necessary to correct the GIR for urinary loss of glucose, and the clamp results are then more appropriately expressed as $SIC_{\text{clamp}}$ [17].

The HIEG clamp test has generated a vast amount of valuable information. However, it has three major disadvantages: (1) it requires two intravenous catheters, calibrated pumps and online glucose-level determination; (2) it requires trained staff; and (3) it is time-consuming, thereby precluding its use in large cohorts [11]. In addition, the absence of standardization of important parameters, such as duration of the procedure, insulin infusion rate and normalization of the GIR, precludes comparisons across studies [26].

The glucose clamp procedure is a reliable test for assessing insulin secretion. To do this, the hyperglycaemic clamp was developed. The procedure involves infusing glucose to rapidly achieve hyperglycaemia. Then, as with the HIEG clamp, the glucose infusion is adapted to maintain the level of hyperglycaemia at usually 200 mg/dL (11.0 mmol/L). The
hyperglycaemic clamp allows evaluation of both the early and late phases of insulin secretion, and permits the assessment of insulin sensitivity/resistance by calculation of M/I, as with the HIEG clamp [22]. However, this method is less precise than the HIEG clamp for comparing insulin action between subjects with wide variations in endogenous insulin secretion rates and/or variable fasting glucose levels.

2.2. Insulin suppression test

The insulin suppression test (IST), described by Shen et al. [27], is another method that directly measures insulin sensitivity/resistance. After an overnight fast, somatostatin (250 µg/h) is intravenously infused to suppress the endogenous production of insulin. At the same time, glucose (6 mg/kg body weight/min) and insulin (50 mU/min) are infused over 150 min at a constant rate. Glucose and insulin determinations are performed every 30 min for 2.5 h, then at 10 min intervals from 150 to 180 min of the IST. The resulting SSPG concentration obtained during the last 30 min of infusion represents an estimation of tissue insulin sensitivity. The higher the SSPG concentration, the more insulin-resistant the individual is. The IST was the first test to use steady-state plasma insulin levels to promote disposal of a glucose load.

However, as with the HIEG clamp, the IST is difficult to apply in large epidemiological studies. Furthermore, there is a risk of hypoglycaemia in insulin-sensitive subjects. Moreover, the IST could provoke glycosuria in some subjects, such as type 2 diabetic patients, and could then lead to underestimation of insulin resistance by SSPG.

2.3. Minimal model analysis of frequently sampled intravenous glucose tolerance test

This method, described by Bergman et al. [28], gives an indirect measurement of insulin sensitivity/resistance based on the glucose and insulin values obtained during a frequently sampled intravenous glucose tolerance test (FSIVGTT), and is associated with a mathematical model that integrates the glucose–insulin relationships. The minimal model uses the kinetics of increasing circulating insulin and decreasing circulating glucose to obtain two different indices—namely, the SiMM (insulin sensitivity index) and SgMM (glucose effectiveness index) [14,29]. The SiMM index—which represents the link between insulin levels and its effect, glucose disappearance from plasma—provides information on peripheral and liver insulin sensitivity/resistance. On the other hand, the SgMM gives information on the effects of glucose on its own disappearance independent of any insulin variation [29].

In addition to the insulin sensitivity index, the FSIVGTT also derives two indices of insulin secretion (early phase and late phase) from a single test. However, as with the HIEG clamp, the minimal model is complex because it requires two venous catheters, and blood must be sampled very frequently over 3–4 h, even when a reduced sampling schedule has been applied [30]. The test also depends on specific software. Moreover, in individuals with significantly impaired insulin secretion and/or major insulin resistance, such as type 2 diabetic patients, the ‘standard’ minimal model is less reliable. In this case, the minimal model analysis of FSIVGTT modified by exogenous insulin infusion allows the assessment of insulin sensitivity/resistance [31].

However, as these sophisticated methods are not easily performed in large populations, surrogate indices for insulin sensitivity/resistance assessment have been developed.

3. Simple surrogate indices of insulin sensitivity/resistance

3.1. Indices derived from OGTT values

The oral glucose tolerance test (OGTT) is a simple test that is widely used in clinical settings for the diagnosis of glucose intolerance and type 2 diabetes. Whereas, for clinical diagnosis, fasting and 2 h postload glucose values are sufficient, additional samples for both plasma insulin and glucose obtained every 30 min following an oral glucose load (75 g) can allow estimation of insulin sensitivity and/or secretion [32]. The oral route of glucose delivery is clearly more physiological than is either intravenous glucose injection or continuous insulin infusion during an HIEG clamp. However, it remains far from a classical meal situation. To estimate insulin resistance, several surrogate indices incorporate plasma glucose and insulin values during the OGTT into mathematical equations while, in some cases, other parameters, such as weight, BMI and glucose volume of distribution, are used [32–41]. The most frequently used indices are summarized in Table 1. They have usually been validated against the HIEG as the gold-standard method.

The Matsuda index was first described by Matsuda and DeFronzo [32] in subjects with a wide range of glucose tolerance. Fasting glucose and insulin values mainly reflect hepatic insulin sensitivity, whereas mean OGTT values reflect insulin sensitivity in peripheral skeletal muscle. More recently, the same group proposed different formulas for more specifically evaluating hepatic and muscle insulin resistance [42].

The Stumvoll index was derived from a multiple linear-regression model evaluating the effect of different demographic and OGTT parameters, and was also correlated with the clamp. Using plasma insulin values at 120 min and plasma glucose values at 90 min during OGTT, and incorporating BMI into the formula, Stumvoll et al. [33] obtained good correlation with the clamp test.

In the same way, the Avignon index used glucose and insulin concentrations at T0 and T120, incorporating estimates of glucose volume of distribution (VD = 150 mL/kg body weight), and was compared to the Bergman minimal model measure of insulin sensitivity [36]. Belfiore et al. [35] used the area under the curve (AUC) of insulin and glucose during OGTT, and the Gutti index, adapted from the Cederholm index, omitted the constant terms and, instead, used plasma glucose and insulin concentrations at T0 and T120 [34,37]. The oral glucose insulin sensitivity (OGIS) index, developed by Mari et al. [38], is more complex, as it requires the use of two primary
to express glycaemia (mg/dL or mmol/L). Nevertheless, it is possible to easily calculate the OGIS index through the website given in Table 1.

More recently, Vangipurapu et al. [39] used regression analysis to develop a new index that combines insulin values during an OGTT with HDL cholesterol and clinical measurements, such as percentage of fat mass and BMI. This index, called the ‘liver insulin resistance’ (liver IR) index, correlated well with the clamp and, more particularly, with the endogenous glucose production measured by labelled glucose isotopes during the HIEG clamp, which is representative of liver insulin resistance [39].

These indices correlate well with the HIEG clamp and have been validated in different populations. However, not only insulin sensitivity per se, but other biological processes can also affect plasma patterns of glucose and insulin after glucose ingestion. These include the rate of glucose absorption, and endogenous insulin secretion in response to glucose and incretins, as well as insulin-independent effects of glucose on glucose uptake and production [43]. Thus, in contrast to insulin sensitivity measured by the HIEG clamp, insulin sensitivity estimated from OGTT-derived indices could potentially be confounded by physiological factors other than insulin resistance itself. However, OGTT-derived indices depend on the reproducibility of OGTT, which is variable due to interindividual variability of glucose absorption and interindividual differences in incretin action on insulin secretion. Nevertheless, OGTT-derived indices have the advantage of being able to evaluate several parameters during the same test, including glucose tolerance, insulin sensitivity and insulin secretion. However, these indices are all more complex than fasting indices, and require at least 2 h of testing.

More recently, the present team developed a new, additional index derived from the OGTT (SI<sub>OGTT</sub>) [40]. This involved taking into consideration the data reported by Cheng et al. [44] indicating that the log transformation of the sum of insulin concentrations, together with the sum of glucose concentrations during OGTT, were highly correlated with the HIEG clamp expressed as either M, M/I, M<sub>FFM</sub> or M<sub>FFM</sub>/I. Thus, by making an analogy with the quantitative insulin-sensitivity check index (QUICKI, see below), we proposed a simple formula (Table 1) that correlates well with the HIEG clamp in the nonobese, obese/overweight postmenopausal female population, however, the clamp results are expressed [40]. The SI<sub>OGTT</sub> index was recently validated in a group of middle-aged sedentary men [45] and in nonobese, nonobese healthy subjects [46].

Two recent studies systematically compared surrogate indices, including OGTT and fasting-derived indices, with the gold-standard HIEG clamp, and examined the relationship between these different assessments of insulin sensitivity/resistance with CVD risk factors [47,48]. It was demonstrated that the association between various surrogate indices, including those derived from both fasting (HOMA, QUICKI) and OGTT (Matsuda index, Stumvoll index and SI<sub>OGTT</sub>) measurements, and cardiometabolic risk factors can vary widely from one index to another [48], although Lorenzo et al. [47] found different results. They showed that surrogate indices, including those derived from fasting measurements,
were reliable measures of insulin resistance and similar in their relationships to metabolic abnormalities, including definitive measures of fat distribution. However, three OGTT-derived indices (Matsuda index, Avignon index and SIisOGTT) were better correlated with the HIEG clamp [47]. Moreover, they also concluded that surrogate indices, including those derived from fasting measurements, are valid measures of insulin resistance, and that OGTT with multiple sampling is not necessary for estimating insulin sensitivity/resistance in both clinical and epidemiological studies [47].

Although several indices derived from OGTT are currently available and provide important information on insulin-resistance status, the absence of reference range values for these indices limits their use in clinical practice. Furthermore, most of these indices still need to be validated in large cohorts of subjects with wide ranges of insulin sensitivity and glucose tolerance before considering their use in clinical practice.

3.2. Indices derived from fasting values

The fasting condition, in healthy subjects, represents a steady state, with glycaemia tightly maintained between normal values as the result of the effect of insulin on HGP, which equals whole-body glucose disposal upon fasting. Under such conditions, plasma insulin levels will vary according to the degree of insulin sensitivity. Therefore, surrogate fasting indices that include both glycaemia and insulinemia will permit estimation of insulin resistance in a simple and cost-effective way, although it primarily represents hepatic sensitivity [42]. Also, glucose utilization under fasting conditions is mainly cerebral and is noninsulin-dependent. Yet, what is surprising is that fasting indices have been validated against the gold-standard clamp method, which more specifically measures muscle, rather than hepatic, insulin sensitivity. However, although fasting indices primarily reflect hepatic insulin resistance, they also estimate global insulin resistance. In addition, peripheral insulin resistance and hepatic insulin resistance are closely related [49]. It is possible with the clamp method to measure hepatic insulin sensitivity/resistance, but this requires the use of labelled glucose, which makes the test more complicated and laborious than the classical HIEG clamp.

Another point that should be mentioned is that the use of arterialized blood is recommended for blood glucose measurement by glucolamine. However, arterialized sampling is never done in clinical practice for calculation of fasting indices and, thus, might influence the relationship between fasting surrogate indices and clamp results. Nevertheless, as mentioned above, the results obtained from venous and arterialized blood measurements are roughly comparable, and the differences are most likely small enough to be comparable to those found in fasting measurement variability and, thus, unlikely to alter the relationship.

Homeostasis model assessment (HOMA) and QUICKI are the most widely used indices based on fasting parameters [50,51]. The HOMA, first described in 1985 [50], is the result of a computed model in which fasting glucose and insulin values are plotted to allow assessment of the expected β-cell response and insulin resistance with each pair of values. The HOMA formula is a simplification of this mathematical model, and can be described as the product of fasting glucose and fasting insulin divided by a constant: HOMA = [(fasting insulin (µU/mL)) × (fasting glucose (mmol/L))] /22.5. The denominator reflects normalization, based on normal fasting values as the result of the product of 5 µU/mL insulin levels and 4.5 mmol/L glucose levels.

As insulin secretion follows a pulsatile pattern, the use of the mean of three samples taken at 5 min intervals, instead of a single sample, to compute the HOMA score has been recommended [50]. However, a single sample, which has often been used in practice, provides an acceptable compromise and yields similar results in large datasets [52]. Nevertheless, for a given individual, the use of a single sample results in intrasubject coefficients of variation that are higher than when three samples are used [52]. In this circumstance, the use of the mean insulin concentration from three samples is preferable.

HOMA has proved useful in large epidemiological studies by demonstrating good correlations with HIEG clamp results in several populations. Interestingly, the HOMA of beta-cell function (HOMA-β) is a complementary formula that allows estimation of insulin secretion [50], while the addition of anthropometric measurements such as BMI is able to improve the reliability of HOMA for estimating insulin sensitivity. Indeed, to identify insulin-resistant patients, Stern et al. [53] developed decision rules from measurements of obesity, fasting glucose, insulin and other metabolic parameters in 2321 individuals, who participated in an HIEG clamp study at several European and USA sites. Distribution of whole-body glucose disposal appeared to be bimodal, with an optimal insulin resistance cut-off value of < 28 µmol/kgLBM/min. Using recursive partitioning, the authors also developed several types of classification tree models. One was of particular interest as it generated the simple decision rule of an insulin-resistance diagnosis if any of the following conditions were present: BMI > 28.9 kg/m², HOMA-IR (insulin resistance) > 4.65, or BMI > 27.5 kg/m² and HOMA-IR > 3.60, with a sensitivity of 84.9% and a specificity of 78.7%, respectively [53].

However, the original contributors of the HOMA index have pointed out some limitations of such simplification of the mathematical model [52,54]. For this reason, the HOMA software has been recently updated and is currently available as HOMA2 on the Oxford University website (www.dtu.ox.ac.uk/homacalculator/index.php), and now allows the estimation of steady-state beta-cell function (%B) and insulin sensitivity (%S) as percentages of a normal reference population. Although the use of HOMA-B and HOMA-S does not definitively classify a subject as insulin-resistant or insulin-deficient, it may offer information to help the clinician to decide which first-line therapy to use. Moreover, such information may be of interest in cases of severe insulin resistance syndromes by identifying such a state.

Based on the same physiological principle, the QUICKI index is similar to HOMA by being its inverse logarithm. Described by Katz et al. [51] in a heterogeneous population (nonobese, obese and type 2 diabetics), good correlations were
observed between fasting values and HIEG clamp results with QUICKI, as with HOMA [49]. As fasting insulin levels are not normally distributed, their log transformation improves linear correlation with the HIEG clamp. Thus, the QUICKI formula is: 1/[log (I0 μU/ml) + log (G0mg/dl)] [51]. QUICKI has been extensively validated in different populations and is reasonably correlated with the HIEG clamp [51,55–59].

Comparison of these two fasting indices has been the subject of many publications. Chen et al. [57] demonstrated, in a cohort of normal, obese, hypertensive and diabetic subjects, that QUICKI and log(HOMA) had better predictive power than fasting insulin, different expressions of HOMA and the insulin sensitivity index derived from the minimal model (SI(MM)). Indeed, log transformation of the HOMA formula can further improve its linear correlation with the HIEG clamp [55]. On the other hand, Vaccaro et al. [60] could find no difference between the QUICKI and HOMA in evaluating insulin resistance assessed by the FSIVGTT, nor in identifying subjects with a metabolic syndrome.

Evidently, there is no apparent difference between these two indices, as both are based on the same underlying physiological principles. More specifically, HOMA and QUICKI exhibit equivalent coefficients of variation when the HOMA is correctly log-transformed [61]. On the other hand, the usefulness of the HOMA and QUICKI is limited in pathophysiological situations such as insulinoma and primary hyperaldosteronism [62]. Their relevance has been reported to be weak in nondiabetic subjects and in specific ethnic groups such as Japanese subjects, in whom OGTT-derived indices appear to better correlate with insulin-resistance measurements [63–65]. In addition, the reliability of these indices to estimate insulin sensitivity may depend on the subject’s insulin-sensitive status, as noted by Ferrara and Goldberg [66], who reported weaker correlations for those with impaired glucose tolerance (fasting glucose: <5.6 mmol/L, 2 h glucose: 7.8–11.1 mmol/L) than for subjects with normal glucose tolerance (fasting glucose: <5.6 mmol/L, 2 h glucose: <7.8 mmol/L) in a middle-aged (47–74 years) cohort.

However, in general, the relevance of fasting-derived indices has been shown to be weaker in healthy populations, and several authors have reported that fasting insulin is merely an acceptable surrogate for estimating insulin sensitivity [67,68]. In fact, while healthy subjects may exhibit a wide range of insulin-sensitivity levels, fasting glucose and insulin values are maintained within narrow ranges, thus explaining the poorer performance of fasting-derived surrogates in estimating insulin sensitivity in clinically healthy subjects. This suggests that small, but clinically relevant, variations in insulin sensitivity may be overlooked by simple indices and, thus, need to be identified by more sophisticated methods, such as the HIEG clamp or other direct and dynamic measures of insulin sensitivity.

To enhance the sensitivity and specificity of fasting-derived indices in estimating insulin sensitivity and identifying insulin-resistant subjects, several groups have either developed new indices, or proposed modified formulas for commonly used indices by including additional fasting metabolic parameters, especially lipids.

Perseghin et al. [69] added the log of the fasting value of non-esterified fatty acids (NEFA) to the QUICKI formula. The rationale for such modification was that the effect of insulin on lipolysis occurs at lower levels than its effects on glucose metabolism [2]. Thus, by estimating the antilipolytic effect of insulin, fasting NEFA concentrations can reflect insulin resistance earlier than do fasting glucose values.

This revised QUICKI formula improved its correlation with HIEG clamp data in healthy subjects and in healthy type 2 diabetes offspring [69], and was further confirmed by two independent teams [70,71]. The present authors also observed an improved performance with the revised QUICKI in a wide spectrum of pathophysiological states [70]. Switching NEFA for glycerol, another surrogate of lipolysis, similarly enhanced the QUICKI formula performance [70]. However, despite its potential value, the addition of NEFA to the fasting-derived index formula required a further biochemical measure, and NEFA concentrations may also be dependent on confounding parameters such as dietary interventions and weight loss [72].

McAuley et al. [73] used regression analysis and bootstrap procedures to identify fasting insulin and fasting TG as the most useful variables in the prediction of insulin sensitivity. They proposed an empirical formula—the McAuley index—derived from the regression equation including these two variables: exp {2.63–0.28 ln(fasting insulin (μIU/mL))–0.31 ln(fasting TG (mmol/L))} [73]. Following the same line of thinking, Guerrero-Romero et al. [74] evaluated a similar simple index in subjects with various degrees of glucose tolerance and body weight using just fasting TG and glucose (TyG index = ln(fasting TG (mg/dL) × fasting glucose (mg/dL)/2)). They observed good correlation with the clamp and suggested that this index might be helpful for the identification of subjects with insulin resistance [74].

Recently, our group developed a new fasting-based index in a population of healthy subjects (31 men and 39 women) [75]. Using multiple forward-regression analysis, we determined that fasting NEFA concentrations and the atherogenic index were two reliable variables to further improve the estimation of insulin sensitivity in healthy subjects. Indeed, among the variables tested, fasting insulin, NEFA and the HDL cholesterol/total cholesterol ratio explained 53% of the variation of insulin sensitivity, expressed as MFFM/I. We also derived a simplified formula from the regression equation, the Disse index: 12 × [2.5 × (HDL-cholesterol (mmol/L)/total cholesterol (mmol/L)]–NEFA (mmol/L)]–insulinemia (μIU/mlmL) [75]. The Disse index was highly correlated with MFFM/I (r = 0.79, P < 0.001), and there was good agreement between the two methods. Using a receiver operating characteristic (ROC) curve analysis, we also demonstrated that this formula was the best way to identify insulin-resistant subjects in an apparently healthy population, as it was able to identify 88% of insulin-resistant subjects with 77% specificity [75]. Interestingly, the Disse index is also able to estimate both insulin sensitivity and its improvement following a weight-loss programme in a population of nondiabetic overweight or obese postmenopausal women [76], and it is still relevant for estimating insulin sensitivity in type 2 diabetic patients (personal data), despite the absence
of a glucose value in the formula. However, the impact of the widely prescribed lipid-lowering medications on the accuracy of formulas that include lipid parameters remains to be determined.

4. Choosing a method to measure or estimate insulin sensitivity

Numerous factors have to be taken into account when selecting a way to measure or estimate insulin sensitivity. Among these factors, the nature of the study population and the question that is being asked are the main indicators. However, different methods also require, for example, different time considerations, sample numbers and costs that will ultimately influence the choice. In addition, the different methods allow the investigation of different aspects of glucose homeostasis and different components of insulin sensitivity/resistance. Thus, knowledge of the underlying mechanisms that can explain the results obtained with the different methods is of major importance. Moreover, it should be remembered that numerous factors are thought to influence insulin sensitivity, such as recent physical exercise and food intake. Therefore, it is important to develop a method of standardization to control dietary intake, physical activity and duration of fasting prior to the use of any methods (surrogate or direct measures of insulin sensitivity/resistance) to assess insulin resistance [77].

When exploring insulin sensitivity in research protocols, the HIEG clamp—and, to a lesser extent, its hyperglycaemic version—remain the gold-standard method for the direct measurement of insulin sensitivity. Depending on the clamp protocol used (insulin infusion rate, use of stable metabolic tracers), it is possible to assess tissue-specific insulin sensitivity in muscle, liver and adipose tissue [11–18]. In addition, the HIEG clamp can be used in all types of populations, including diabetic patients, although the situation is more complex in such patients and calls for a choice between clamping at euglycaemia or isoglycaemia, as already discussed in the clamp section above. The IST also allows the assessment of insulin resistance in various populations, including diabetic patients, but is not able to assess the tissue specificity of insulin sensitivity. The FSIVGTT, which allows assessment of both insulin sensitivity and glucose-stimulated insulin secretion, is impractical in subjects with major impaired insulin secretion (type 1 and 2 diabetic patients), does not differentiate the tissue specificity of insulin sensitivity and requires technical resources as major as those for an HIEG clamp.

OGTT-derived indices offer several reliable types of information within a simple test: glucose tolerance, insulin resistance and insulin secretion. However, when specifically exploring insulin sensitivity, the OGTT is not as precise as the HIEG. In addition, although OGTT-derived indices can be used in larger populations than the sophisticated methods described above, the number of OGTT-derived formulas without a well-accepted reference formula limits comparisons between studies. Indeed, no one formula appears to be significantly superior to the others [48], despite some of them being better correlated with the HIEG clamp [47].

In spite of their wide use in research, fasting-derived indices remain imperfectly validated in numerous populations and situations. However, they are easy to calculate, which explains their popularity. For large groups of subjects, such as in epidemiological studies, they offer an easy-to-use tool for determining any differences in insulin-sensitivity status between groups. They may also be relevant for estimating global cardiometabolic risk, as insulin sensitivity/resistance assessed by these indices has been shown to correlate with the intima–media thickness of the carotid artery [78], a well-accepted surrogate of atherosclerosis. They are also relevant in the prediction of type 2 diabetes [79] and the occurrence of cardiovascular events [80].

Nevertheless, it is important to note that, in clinical practice, assessing the level of insulin sensitivity using the different methods presented in this review is not currently recommended. Indeed, the identification of the classical risk factors (such as glycaemia, blood pressure, lipid profile, BMI and waist circumference) included in the various definitions of the metabolic syndrome remains, at present, satisfactory for guiding any therapeutic approaches.

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