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Measurement of Insulin Resistance *In Vivo*

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Abstract

Insulin sensitivity, which can be impaired in both glucose-intolerant and non–glucose-intolerant individuals, is a valuable parameter because of its potential as a marker for the future development of diabetes and increased cardiovascular risk. Techniques available for the determination of insulin sensitivity include the glucose clamp, insulin tolerance test, insulin suppression test, the frequently sampled intravenous glucose tolerance test and the regional artero-venous balance. Model assessment methods are also available for the measurement of insulin sensitivity at steady-state plasma glucose and insulin levels or after a standardised glucose infusion. Methods vary in their complexity, and the choice between them depends on the nature of the information required. There is also evidence for a strong genetic contribution to insulin sensitivity; although identification of the relevant gene(s) has not yet been successful, accurate phenotyping should still be carried out as part of the assessment of a patient's clinical status.

1. The Need for a Measurement of Insulin Action *In Vivo*

Insulin resistance is common in individuals with type 2 diabetes mellitus, and this phenomenon is implicated as a major factor in the development of overt hyperglycaemia. In the Insulin Resistance and Atherosclerosis Study (IRAS), Haffner and coworkers[1] reported that insulin resistance was present, with no variations associated with ethnic or geographical origin, in more than 85% of the individuals with diabetes who were enrolled.

Insulin action is impaired in conditions that are not necessarily associated with glucose intolerance. DeFronzo and Ferrannini[2] have repeatedly shown that patients with type 2 diabetes, obese nondiabetic individuals, and patients with essential hypertension may all have the same degree of insulin resistance relative to individuals with normal insulin sensitivity. Hollenbeck and Reaven[3] demonstrated a wide range of insulin sensitivities in their work in 100 normal individuals. Division of rates of glucose uptake in response to the action of insulin into quartiles showed that those falling in the lowest quartile had insulin sensitivities as low as those observed in the most insulin resistant of patients with type 2 diabetes. Low insulin sensitivity in nondiabetic individuals is associated with metabolic alterations linked to syndrome X[4] (insulin resistance syndrome[2]). This association is fully apparent in the database collected by the European Group of Insulin Resistance (EGIR), which includes 1200 euglycaemic hyperinsulinaemic (1 mU/kg/min insulin infusion) clamp studies performed in nondiabetic individuals across 9 European countries. Even in individuals with a body mass index (BMI) ≤27 kg/m^2, those in the lowest

Table I. Features of the most common tests for the assessment of insulin sensitivity *in vivo*

Property	Glucose clamp	Insulin tolerance test	Insulin suppression test	Regional A-V balance	FSIVGTT	HOMA, CIGMA
Quantitative	Yes	No	No	Yes	Yes	No
Noninvasive	Yes	Yes	Yes	No	Yes	Yes
Simple	+	+++	++		++	Yes
Economical	No	Yes	Yes	No	No	Yes
Physiological	++		+	++	++	++
Reproducible	++	++	+	++	++	++
Mechanism(s) interpretation	Yes	No	No	Yes	Yes[a]	No
Correlation with the insulin sensitivity index derived from the clamp		Good	Good	Good	Good	Good

a With tracer.

A-V = artero-venous; **CIGMA** = constant infusion of glucose with model assessment; **FSIVGTT** = frequently sampled intravenous glucose tolerance test; **HOMA** = homeostatic model assessment; +, ++ and +++ indicate increasing concordance with the properties shown.

quartile of insulin sensitivity (M value = 19.9 ± 0.4 μmol/kg/min) had higher systolic and diastolic blood pressures and higher plasma triglyceride and cholesterol levels than those in the highest quartile (M value = 53.5 ± 0.5 μmol/kg/min).[5]

This brief analysis supports the view that insulin sensitivity can be a valuable parameter, not only in diabetes mellitus and other pathological states but also in individuals without diabetes. This is because it may be a marker for the future development of diabetes and increased cardiovascular risk.

2. Measurement of Insulin Sensitivity *In Vivo*

Over time, a number of tests have been developed to measure insulin action *in vivo*;[6-8] table I summarises some features of the tests most commonly used.

The glucose clamp is regarded as the gold standard in the assessment of insulin action. This technique has generated the largest amount of valuable and reproducible information, and is characterised by its flexibility. It can be carried out with any combination of plasma insulin and glucose concentrations, which enables researchers to focus on specific aspects of insulin action (sensitivity *vs* responsiveness, liver *vs* peripheral tissues etc.). Moreover, the glucose clamp can be combined with a variety of other techniques (e.g. tracers, indirect calorimetry or regional tissue sampling). The main drawbacks of this method are the need for dedicated equipment and trained personnel. In addition, clamp conditions (very high plasma insulin concentrations with normal glucose levels) do not imitate normal physiological states.

The insulin tolerance test (ITT) is much easier to carry out and provides an index [the rate constant for the decline in blood glucose concentrations (k_{ITT})] but not a quantitative measure of insulin-mediated glucose disposal. The k_{ITT} correlates with the clamp-derived estimate of insulin sensitivity. However, the test employs pharmacological doses of insulin and it may cause hypoglycaemia; concomitant neurological and cardiovascular adverse effects are the major sources of concern with this method.

In the insulin suppression test, glucose and insulin are infused while endogenous insulin secretion is suppressed by epinephrine (adrenaline). Propranolol is infused at the same time to suppress the metabolic effects of adrenaline (i.e. stimulation of endogenous glucose production). However, the propranolol block of epinephrine may be incomplete, which may trigger disturbance of cardiac rhythm.

The frequently sampled intravenous glucose tolerance test (FSIVGTT) with minimal model analysis provides a quantification of insulin sensitivity, although it requires a discrete insulin response and its performance deteriorates in the presence of severe insulin resistance. Combination

with glucose tracers permits elucidation of both production and utilisation of glucose.

The regional artero-venous balance (forearm A-V balance) provides a direct assessment of glucose utilisation by specific tissues or organs. This technique is invasive, however.

Insulin sensitivity can be determined from steady-state plasma levels of glucose and insulin by homeostatic model assessment (HOMA) or after standardised glucose infusion by constant infusion of glucose with model assessment (CIGMA). Although these approaches may appear much simpler, particularly for epidemiological purposes, the relationship between the insulin sensitivity index (*R*) and insulin-mediated glucose disposal measured with the glucose clamp technique is not readily comparable. Moreover, the site of insulin resistance remains undetermined.

The choice of a test depends upon several considerations; however, a hypothetical correlation can be drawn to relate the complexity of the test to the quality and quantity of information generated. Generally speaking, the more complex the test the more informative the results. The choice of method for the assessment of insulin sensitivity is ultimately a function of the information required. In accordance with this view, most epidemiological investigations have been carried out with simple methods (e.g. fasting plasma insulin levels), although more informative tests have been employed recently. Although retrospective, the EGIR database represents the largest collection to date of clamp results from nondiabetic individuals and has provided interesting information on the relationship between insulin action and age,[9] obesity,[10] hypertension[11] and the metabolic syndrome.[4] The FSIVGTT is currently being used in the IRAS.[1] As already mentioned, the main drawback of this approach is the difficulty in obtaining data in the presence of sluggish insulin responses and severe insulin resistance. Thus, as many as 15% of IRAS assessments yielded insulin sensitivity indices equal to zero. The tests seem to perform better when carried out in young, healthy people, as in a Danish survey.[12]

3. Phenotype and Genotype of Insulin Action in Humans

Data are available to indicate a strong genetic contribution to the determination of insulin action in any given individual.[12] Nevertheless, attempts to identify the relevant gene(s) have not been successful to date, and it is likely that accurate phenotyping could assist in this respect.

The rate of glucose utilisation in response to insulin is a function of the response of several insulin-sensitive tissues. A generic measure of insulin sensitivity will therefore not allow the identification of the relative contributions of individual tissues to overall insulin action. This is of particular importance in the light of growing evidence that whole-body insulin resistance can stem from a tissue-specific defect.[13-15] This original defect is difficult to detect because of accommodation processes involving several tissues. Thus, the more advanced the process the smaller the chance of identifying the primary change (i.e. that with the predominant genetic influence).

On the basis of this brief discussion, we may conclude that, if accurate phenotyping can assist in the identification of the genetic basis for insulin action, the latter should be measured in humans in such a way that specific information on insulin action at the level of individual insulin-responsive tissues may be provided. Moreover, in order to address the primary defect, a phenotype description should be obtained before the patient's clinical status is fully developed.

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