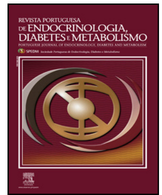
Rev Port Endocrinol Diabetes Metab. 2014;9(1):65–73

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.elsevier.pt/rpedm



Revisão

Assessment of methods and indexes of insulin sensitivity

Rita S. Patarrão[a,*], Wilford Wayne Lautt[b], Maria Paula Macedo[c,d]

[a] CEDOC, Área de Ensino e Investigação de Medicina Celular e Molecular, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, 1169-056 Lisboa, Portugal
[b] Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba R3E OW3, Canada
[c] CEDOC, Departamento de Fisiologia, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, 1169-056 Lisboa, Portugal
[d] APDP-ERC Portuguese Diabetes Association Education and Research Center, Rua do Salitre, 118-120, 1250-203 Lisbon, Portugal

ARTICLE INFO

Article history:
Received 5 September 2012
Accepted 22 October 2013
Available online 14 March 2014

Keywords:
Hyperinsulinemic Euglycemic Glucose Clamp
Oral Glucose Tolerance Test
Meal Tolerance Test
Rapid Insulin Sensitivity Test
Homeostasis Model Assessment
Oral Glucose Insulin Sensitivity

ABSTRACT

Insulin resistance contributes to the pathophysiology of diabetes and is a hallmark of obesity, metabolic syndrome, and many cardiovascular diseases. Therefore, quantifying insulin sensitivity/resistance in humans and animal models is of great importance.

Various methods are used to assess insulin sensitivity both in individuals and in study populations. Validity, reproducibility, cost, and degree of subject burden are important factors for both clinicians and researchers to consider when weighing the merits of a particular method. Some methods rely on steady-state analysis of glucose and insulin, whereas others rely on dynamic testing. Each of these methods has distinct advantages and limitations. Thus, optimal choice and employment of a specific method depend on the nature of the studies being performed. Established direct methods for measuring insulin sensitivity *in vivo* are relatively complex. Finally, simple surrogate indexes for insulin sensitivity/resistance are available that are derived from blood insulin and glucose concentrations under fasting conditions (steady state) or in the postprandial state (dynamic). This article highlight merits, limitations, and appropriate use of current *in vivo* measures of insulin sensitivity/resistance and presents the advantages and disadvantages of each.

© 2012 Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo. Published by Elsevier España, S.L. All rights reserved.

Métodos de avaliação e índices de sensibilidade à insulina

Palavras-chave:
Clamp de glucose hiperinsulinémico e euglicémico
Teste oral de tolerância à glucose
Teste de tolerância à refeição
Teste rápido de sensibilidade à insulina
Avaliação do modelo de homeostase
Glucose oral e sensibilidade à insulina

RESUMO

A resistência à insulina contribui para a fisiopatologia da diabetes e é uma característica marcante da obesidade, da síndrome metabólica, e de doenças cardiovasculares. Assim, quantificar a sensibilidade à insulina *vs* resistência à insulina em humanos e em modelos animais é de grande importância.

Existem vários métodos para avaliar a sensibilidade à insulina, tanto em indivíduos, como em populações de estudo. A validade, reprodutibilidade, custo e envolvimento dos indivíduos são fatores importantes a considerar para os clínicos e investigadores aquando da escolha de um determinado método de avaliação da sensibilidade e/ou resistência à insulina. Alguns métodos dependem da quantificação dos níveis de glucose e de insulina no estado estacionário, embora outros métodos possam ser utilizados no estado dinâmico. Cada um destes métodos tem vantagens e limitações distintas. Assim, a escolha e a aplicabilidade correta de um método específico depende da natureza dos estudos a serem realizados. O desenho de métodos diretos para medir a sensibilidade à insulina *in vivo* é relativamente complexo. Existem alguns índices simples para avaliar a sensibilidade e/ou resistência à insulina, que resultam da avaliação das concentrações de insulina e glucose em jejum (estado estacionário) ou no estado pós-prandial (estado dinâmico). Este artigo destaca as limitações e a utilização adequada dos atuais métodos de avaliação de sensibilidade e/ou resistência à insulina e apresenta as vantagens e desvantagens de cada um dos métodos.

© 2012 Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo. Publicado por Elsevier España, S.L. Todos os direitos reservados.

* Corresponding author.
E-mail address: rita.patarrao@fcm.unl.pt (R.S. Patarrão).

1646-3439/$ – see front matter © 2012 Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo. Published by Elsevier España, S.L. All rights reserved.
http://dx.doi.org/10.1016/j.rpedm.2013.10.004

Introduction

Measurements of insulin sensitivity provide clinicians and researchers with excellent instruments to objectively evaluate the efficiency of both current and potentially useful interventional tools.

It is of great importance to develop tools for quantifying insulin sensitivity/resistance in humans, which may be used to appropriately investigate the epidemiology, pathophysiologic mechanisms, outcomes of therapeutic interventions, and clinical course of patients with insulin resistance.

Methods of insulin sensitivity/resistance assessment

Hyperinsulinemic Euglycemic Glucose Clamp

The Hyperinsulinemic Euglycemic Clamp (HIEC), originally developed by DeFronzo, is widely accepted as the "gold standard" for directly determining metabolic insulin sensitivity in humans.[1] After an overnight fast, insulin is infused intravenously at a constant rate that may range from 5 to 120 mU/m^2/min (dose per body surface area per minute, during 180 min). This constant insulin infusion results in a new steady-state insulin level that is above the fasting level (hyperinsulinemic). Consequently, glucose disposal in skeletal muscle and adipose tissue is increased while hepatic glucose production (HGP) is suppressed. Under these conditions, a glucose analyzer is used to frequently monitor blood glucose levels at 5–10 min intervals, while 20% dextrose is given intravenously at a variable rate in order to "clamp" blood glucose concentrations in the normal range (euglycemic). After several hours of constant insulin infusion, steady-state conditions are typically achieved for plasma insulin, blood glucose, and the glucose infusion rate (GIR). Assuming that the hyperinsulinemic state is sufficient to completely suppress HGP, and since there is no net change in blood glucose concentrations under steady-state clamp conditions, the GIR must be equal to the glucose disposal rate (*M*). Thus, whole body glucose disposal at a given level of hyperinsulinemia can be directly determined. *M* is typically normalized to body weight or fat-free mass to generate an estimate of insulin sensitivity. Alternatively, an insulin sensitivity index (*SI*) derived from clamp data can be defined as $SI_{Clamp} = \frac{M}{G \times \Delta I}$, where *M* is normalized for *G* (steady-state blood glucose concentration) and ΔI (difference between fasting and steady-state plasma insulin concentrations).[2]

The validity of glucose clamp measurements of insulin sensitivity depends on achieving steady-state conditions. "Steady-state" is often defined as a period greater than 30 min (at least 1 h after initiation of insulin infusion) during which the coefficients of variation for blood glucose, plasma insulin, and GIR are less than 5%.[2] It is possible to use a radiolabeled glucose tracer under clamp conditions to estimate hepatic glucose production, so that appropriate corrections can be made to *M* in the event HGP is not completely suppressed.[3–5] An alternative approach is to use an insulin infusion rate sufficiently high to completely suppress HGP according to the insulin sensitivity/resistance of the population to be studied.

M is routinely obtained at only a single insulin infusion rate, and therefore comparisons between *M* or SI_{Clamp} among different subjects is valid only if the same insulin infusion rate is used for all subjects.

The principal advantage of the glucose clamp in humans is that it directly measures whole body glucose disposal at a given level of insulinemia under steady-state conditions. Conceptually, the approach is straightforward but there is a limited number of assumptions that are clearly defined. In research settings where assessing insulin sensitivity/resistance is of primary interest and feasibility is not an issue, it is appropriate to use the glucose clamp technique.

The main limitations of the HIEC approach are that it is time-consuming, labor intensive, expensive, and requires an experienced operator to manage technical difficulties. Another limitation is that the clamp utilizes steady-state insulin levels that may be supraphysiological. This results in a reversal of the normal portal to peripheral insulin gradient. Thus, the glucose clamp may not accurately reflect insulin action and glucose dynamics under physiological conditions that a dynamic test, such as, an oral meal or oral glucose load may determine. Further, in the HIEC insulin sensitivity is measured only under a steady-state condition, and therefore, the test does not realistically portray dynamic conditions such as those occurring after normal meals. Because HIEC is dependent on steady-state conditions, insulin infusion is continuous for ≈3 h, and the subjects are in the fasted state. The results of the HIEC may be limited by these restraints, because insulin release is pulsatile,[6–8] and insulin action is sensitized in the postprandial state.[9] Nevertheless, it should be remembered that the HIEC measures insulin-stimulated glucose disposal only at insulin levels in the upper physiological range; information on the effects of insulin on glucose uptake and production in the basal condition, which is physiologically very important, is not provided (unless tracers are used).[10]

Insulin Tolerance Test

The Insulin Tolerance Test (ITT) was one of the first methods developed to assess insulin sensitivity *in vivo*.[11] In this method, a fixed bolus of regular insulin (0.1 IU/kg bw) is given iv after an 8–10 h fast. Blood samples are collected at 15 and 5 min before and 3, 6, 9, 12, 15, 20 and 30 min after insulin injection, and the plasma glucose decrement is then measured. Glucose is injected at 30 min to stop the fall in plasma glucose.[12,13] The faster the decline in glucose concentration, the more insulin sensitive the subject is. The slope of the linear decline in plasma glucose (K_{ITT}) can be calculated by dividing 0.693 by the plasma glucose half-time (50% from baseline):

$$K_{ITT} = \frac{0.693}{t_{1/2}} \times 100$$

where $t_{1/2}$ represents the half-life of plasma glucose decrease, and is calculated from the slope of least square analysis of the plasma glucose concentrations from 3 to 15 min after iv insulin injection, when the plasma glucose concentration declined linearly. Normal K_{ITT} is >2.0%/min and values <1.5%/min are considered abnormal. This method gives an indirect estimate of overall insulin sensitivity.

The advantages of the ITT include its simplicity, rapidity and the use of a bolus injection of insulin. The bolus injection of insulin mimics the physiological pulsatile release of insulin.[6] Furthermore, because glucose tolerance after a meal is dependent on insulin sensitivity, measuring insulin sensitivity in the prandial state is physiologically relevant.

Some of the drawbacks of this method include the supraphysiological insulin dose used, and also the fact that the test does not differentiate peripheral *vs* hepatic insulin resistance.[14] Another major limitation of this test is the risk of hypoglycemia. Hypoglycemia triggers hormonal responses, which may interfere with insulin sensitivity and in turn slows the disappearance rate of glucose from plasma.[15] In this view, the fall in plasma glucose concentration would be a function of the interplay between insulin, on the one hand, and glucagon, catecholamines, growth hormone and cortisol, on the other. Given that, the counterregulatory response occurs only 15–20 min after insulin injection. The glucose fall occurring in the first 15 min after iv insulin administration is probably a

Download English Version:

https://daneshyari.com/en/article/3278347

Download Persian Version:

https://daneshyari.com/article/3278347

Daneshyari.com