Nutrition in Metabolic Syndrome

Module 24.2

Insulin Resistance: Identification and Consequences

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Learning Objectives

• To diagnose insulin resistance;
• To study the role of insulin resistance in cardiovascular disease;
• To identify common features of atherosclerosis and insulin resistance syndrome;
• To study established diabetes and cardiovascular risk.

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   1.4 Other indexes.
2. Insulin resistance: a disease or a physiologic state?
3. Clinical syndromes associated to insulin resistance

Key Messages

1. Insulin resistance can be calculated in a relatively easy way;
2. It is important to know and recognise the limitations for each surrogate index of insulin resistance;
3. Patients insulin resistance diagnosed by these indexes have an increased risk of cardiovascular disease and diabetes;
4. The limitations in these predictions should be interpreted with caution.
1 Practical assessment of insulin resistance

1.1 Methods based on fasting insulin and glucose values
Calculating insulin resistance in euglycemic patients, especially for those at higher risk for type 2 diabetes or cardiovascular diseases by virtue of their race and/or family history, may be essential for effectively planning early interventions to combat cardiovascular disease (1, 2) (Fig. 1, Fig. 2 and Fig. 3).

Figure 1

**Insulin Resistance**

- **Insulin action**: Change in plasma glucose disappearance per unit of insulin concentration.
- **Insulin-resistance (IR)**: when a biological response to insulin, at a given insulin concentration, is under what is considered “normal”.
- **IR** is a decrease in the insulin’s ability to exert its biological actions in target tissues.

Figure 2

1.1.1 Fasting insulin
Fasting insulin concentration (3), the product of serum glucose and insulin or their ratio (4) have been used as surrogate indexes of insulin sensitivity. These indexes show a significant correlation with the gold standard clamp measures in subjects with normal fasting glucose, but they only explain a small fraction of the variability of insulin action (5-25%) (4, 5) (Fig. 4).

This can be easily explained because fasting insulin concentration is determined not only by insulin sensitivity, but also by insulin secretion, distribution and degradation.
Elevated insulin levels reflect insulin resistance. Insulin levels alone do not clearly provide a basis to diagnose insulin resistance, especially in patients with either impaired fasting glucose or with glucose intolerance. As beta cell function declines, plasma insulin levels tend to decrease. When hyperglycaemia is present, the use of hyperinsulinemia as a predictor of insulin resistance is not as accurate.

In a euglycemic patient, a frequently accepted range for normal serum insulin is 3-32 mU/L. Some authors use 17 mU/L as a cut point for insulin levels that indicate insulin resistance (1) (Fig. 5). The pulsatile nature of insulin when physiologically secreted by the pancreas may produce sharp variations in serum insulin concentrations that further complicate the interpretation of the test.

**Practical assessment of insulin resistance**

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- Some authors use 17 mU/L as a cut point for insulin levels that indicate insulin resistance.

**Is so easy?**

**1.1.2 Homeostatic model of assessment (HOMA)**

In HOMA the insulin sensitivity is calculated from the serum glucose and insulin concentrations in equilibrium (or near equilibrium) conditions measured in fasting samples (Fig. 6) (6, 7).

**Practical assessment of insulin resistance**

**HOMA and FIRI**

\[
\text{HOMA} = \frac{\text{glycaemia (mmol/l)}}{\text{insulinemia (mU/l)}}
\]

\[
22.5
\]


\[
\text{FIRI} = \frac{\text{glycaemia (mmol/l)}}{\text{insulinemia (mU/l)}}
\]

\[
25
\]


**Figure 5**

**Figure 6**
The function of HOMA to calculate insulin resistance derives from a model of glucose homeostasis that takes into account the distribution, production, and disposal of glucose. The uptake and production of glucose are assumed to be dependent on glucose concentration, insulin, and insulin resistance index (R). The role of R as a function of production and uptake of glucose corresponds to unity (R=1) in case of normal homeostasis, and greater values indicate both liver and peripheral insulin resistance.

In the calculation of HOMA the measurement of baseline glucose and insulin are enough to detect insulin resistance on a qualitative basis. However, it cannot be guaranteed that 2 subjects with the same value of glucose and insulin show the same insulin sensitivity. Furthermore, in HOMA, the tissue responsible for insulin resistance (the liver or the periphery) remains undetermined, while in euglycemic clamp or in minimal model, is the peripheral insulin sensitivity that is essentially evaluated.

The calculation of HOMA index (3 determinations of fasting glucose and insulin) is as follows:

\[
\text{HOMA-R} = \frac{G_0 \times I_0}{k}
\]

Serum glucose concentration (G₀) should be in (mmol/L) and insulin (I₀) in (mU/L). The value of k has been calculated to be 22,5 (6, 7).

In some studies a limited accuracy of these surrogates of insulin resistance has been described during puberty in obese and lean children at risk for altered glucorregulation (8). Other studies that compare the HOMA value and clamp- or minimal model-derived insulin sensitivity have shown strong correlation ships (9, 10), although weak (11, 12) and not significant associations have also been described (8). These discrepancies should not be interpreted as a failure of the HOMA index, but as an intrinsic differences attributed to this index.

The simplicity and applicability of HOMA make this index one of the most commonly used. Reference values to calculate insulin resistance should be evaluated in each population (90th percentile).

Matthews et al. found in their studies that the range for normal insulin sensitivity using HOMA is 1.21-1.45 and 2.6-2.89 in insulin-resistant individuals. Different authors normally use a HOMA of 2.8-3 as the cut point for insulin resistance among euglycemic individuals (1).

1.1.3 Other fasting indexes

In Table 1 we can see several indexes of insulin resistance calculated from fasting insulin and glucose concentrations (9, 11, 13-18).

1.2 Insulin tolerance test

This was the first method developed to evaluate in vivo insulin sensitivity (19). It is based on the measurement of the slope of glucose decrease after the administration of an insulin bolus (regular insulin, 0.1 U/Kg). Serum glucose concentrations are measured every 5 min, beginning 10 minutes after the bolus, and continuing until the minute 40. The values are plotted in a semi logarithm scale, observing a lineal decrease in the majority of cases. The slope of this line (k_{ITT}) is a surrogate of insulin sensitivity (Fig. 7).
In this model, a monocompartmental model of glucose is assumed, in which insulin promotes its disappearance promoting peripheral tissue uptake of glucose and suppressing endogenous glucose production. Assuming a distribution volume of glucose of 200-250 ml/Kg, the clearance rate of glucose may be calculated. Both \( k_{ITT} \) and the clearance rate correlate with clamp derived measurements (20).

Among the drawbacks of this technique (Fig. 7):

- \( k_{ITT} \) value depends on the time frame used for its calculation, because glucose disappearance is not monoexponential but it is a multi-exponential process (21).
- Pharmacological, and not physiological serum insulin concentrations are reached during the test (approximately 150 nmol/L after injection).
- Hypoglycaemia is the most important inconvenient. Both its neurological and cardiovascular effects, and the counter-regulatory response that antagonizes insulin effects and prevents a correct estimation of insulin sensitivity.

1.3 Methods based on the oral glucose tolerance test (OGTT) (Table 2).

During the OGTT a continuous interplay between \( \beta \)-cell and insulin sensitive tissues exists. Changes in insulin secretion will be rapidly reflected in glucose concentration, and reciprocally, the variations in glucose production or glucose disposal will determine changes in the insulin secretory response. This closed loop makes difficult to infer the physiological status of the \( \beta \)-cell or extra pancreatic tissues from the interpretation of OGTT results.

Hyperglycaemia and hyperinsulinemia during the OGTT indicate insulin insensibility but a firm conclusion on \( \beta \)-cell function cannot be given. On the opposite side, hyperglycaemia and subnormal insulin values are consistent with \( \beta \)-cell dysfunction, but again a firm conclusion on insulin resistance cannot be reached (Fig. 8).
1.4 Other indexes

Other authors have found that the greater the triglycerides/HDL-cholesterol concentration ratio (TG/HDL), the more insulin resistant the patient, and proposed that this value provides an estimate of insulin sensitivity that is as accurate as the fasting plasma insulin concentration and the other surrogate estimates that use measures of fasting plasma glucose and insulin concentration to assess insulin action (22). A TG/HDL cholesterol concentration ratio ≥ 3.5 identified insulin-resistant patients with a reasonable degree of sensitivity and specificity.

As suggested by the authors, measures of plasma lipid concentrations are standardized to a much greater degree than are assays of fasting plasma insulin concentration, so the possibility of finding a specific numeric value that would have clinical utility is much greater in the case of the TG/HDL cholesterol ratio. Of greater significance is the TG/HDL cholesterol concentration ratio not only provides an estimate of insulin resistance, but also identifies patients who have an atherogenic lipoprotein profile that puts them at increased cardiovascular disease risk (22).
Table 1 Insulin resistance indexes obtained from fasting serum insulin and/or glucose

<table>
<thead>
<tr>
<th>index</th>
<th>FORMULAE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin</td>
<td>$I_0$</td>
<td>3</td>
</tr>
<tr>
<td>HOMA</td>
<td>$(I_0 \times G_0) / 22.5$</td>
<td>7</td>
</tr>
<tr>
<td>Fasting insulin resistance index (FIRI)</td>
<td>$(I_0 \times G_0) / 25$</td>
<td>13</td>
</tr>
<tr>
<td>Insulin glucose ratio</td>
<td>$I_0 / G_0$</td>
<td>4</td>
</tr>
<tr>
<td>Raynaud</td>
<td>$40 / I_0$</td>
<td>14</td>
</tr>
<tr>
<td>Bennet</td>
<td>$1/(\log I_0 \times \log G_0)$</td>
<td>18</td>
</tr>
<tr>
<td>QUICKI</td>
<td>$1/(\log I_0 + \log G_0)$</td>
<td>15</td>
</tr>
<tr>
<td>Avignon (Sib)</td>
<td>$10^9/(G_0 \times I_0 \times VD)$</td>
<td>16</td>
</tr>
<tr>
<td>Mc Auley</td>
<td>$e^{[2.63-0.28 \ln(I-0.31 \ln/\text{Tg})]}$</td>
<td>17</td>
</tr>
</tbody>
</table>

$G_0$: Fasting Glucose; $I_0$: Fasting insulin; $VD$: 150ml/weight(Kg).
$Tg$: Triglycerides
Table 2 Insulin resistance indexes obtained from the oral glucose tolerance test

<table>
<thead>
<tr>
<th>FORMULAE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Glucose ratio 120min</td>
<td>$I_{120}/G_{120}$</td>
</tr>
<tr>
<td>Gutt (ISI$_{0, 120}$)</td>
<td>$(m / MPG) / \log MSI$</td>
</tr>
<tr>
<td>Composite</td>
<td>$10^4 / \sqrt{(G_0 \times I_0) \times (MPG \times MSI)}$</td>
</tr>
<tr>
<td>Avignon (Si2h)</td>
<td>$10^8 / (G_{120} \times I_{120} \times VD)$</td>
</tr>
<tr>
<td>Avignon (SiM)</td>
<td>$\left[ (w \times Sib) + Si2h \right] / 2$</td>
</tr>
</tbody>
</table>

$G_0$: Fasting Glycemia; $G_{120}$: Glycemia 120 min after TTOG; $I_0$: Fasting Insulin; $I_{120}$: Insulin 120 minutes after TTOG; MPG: Mean of $G_0$ and $G_{120}$ (mg/dl); MSI: Mean of $I_0$ and $I_{120}$ (μU/ml); $m$: (75000 mg + ($G_0 - G_{120}$) x 0.19 x weight (Kg)/ 120 minutes; $w$: meanSi2h/meanSib.

2. Insulin resistance: a disease or a physiological state?

Insulin resistance is a state in which there is not a proper response to the action of insulin (Fig. 1, Fig. 2 and Fig. 3). At initial stages, while insulin secretion is preserved, no disorders of glucose metabolism occur (23). Obesity and increasing age are two common factors associated with insulin resistance (23-25), although the latter is under debate. Insulin resistance is also related to hypertension and dyslipidemia (24-25). Frequently, patients who present with normal glucose levels are insulin resistant. It has been calculated that approximately 25% of Caucasian subjects are insulin resistant (Fig. 1, Fig. 2 and Fig. 3).

The term “insulin resistance” as it is used in clinical and experimental settings underscores the inability of insulin to promote normal homeostasis of glucose. A suboptimal strength of insulin action demands the presence of higher-than-normal concentrations of insulin in order to maintain normoglycemia and normal utilization of glucose by insulin target tissues. Thus, the term “insulin resistance” implies the existence of metabolic insulin resistance, which reflects an inadequate effect of insulin on glucose metabolism, but does not address other aspects of insulin action. However, insulin, the most potent anabolic hormone in the body, exerts a multitude of effects on lipid and protein metabolism, ion and amino acid transport, cell cycle and proliferation, cell differentiation, and nitric oxide (NO) synthesis.

Prior to the diagnosis of type 2 diabetes, individuals may possess either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). These abnormalities in glucose homeostasis are due to cellular impairments in the action of insulin (Fig. 9).
The presence of either IFG or IGT is termed "prediabetes" by the American Diabetes Association. It is estimated that up to 10 years prior to the development of type 2 diabetes individuals may have prediabetes and begin to develop macrovascular cardiovascular disease (CVD).

Patients with type 2 diabetes are commonly insulin resistant. Many patients who are obese and have type 2 diabetes produce insulin, but their insulin production is not concordant with their reduced insulin action in their cells. Obese individuals experience reduced sensitivity to the actions of insulin in the body as well as in the insulin-sensitive tissues (skeletal muscle, fat, and liver).

Insulin resistance, prediabetes, and type 2 diabetes are thought to be linked together by a similar pathophysiological process. In the first stages, muscle, fat, and liver cells do not use insulin properly. The pancreas compensates by attempting to keep up with the requirements for insulin, by producing more insulin. Therefore, as plasma insulin levels increase, normal levels of glucose are maintained. As time passes, when insulin secretion declines, insulin-resistant individuals develop both elevated levels of blood glucose and insulin.

Altered glucose tolerance places individuals at a higher risk of developing type 2 diabetes and/or CVD (Fig. 10, Fig. 12 and Fig. 13).
Figure 10

Conversion to Type 2 diabetes (7-year incidence)


Figure 12

Mean HDL cholesterol by insulin resistance/secretion category

Research has shown that individuals with altered glucose tolerance develop type 2 diabetes within 10 years and also have an advanced risk of CVD (26).

3. Clinical syndromes associated to insulin resistance

The insulin resistance syndrome is a constellation of abnormalities, including central obesity, glucose intolerance, dyslipidemia, hypercoagulability and hypertension, which promote the development of type 2 diabetes mellitus, cardiovascular disease, cancer, polycystic ovarian disease (PCOS), and nonalcoholic fatty liver disease (Fig. 14).
The disorders associated with insulin resistance, together with endothelial dysfunction, are all likely to be part of the pathogenesis of atherosclerosis. In fact, insulin resistance might directly contribute to endothelial cell dysfunction and atherosclerosis. Activation of the NO pathway by insulin in the endothelial cell, which has beneficial antiatherogenic effects through NO-mediated vasodilation, may be impaired in individuals with insulin resistance (27). The Paris Prospective Study showed that men in the highest quintile of plasma insulin had a ∼2.5-fold higher relative risk for CHD mortality compared with those in the lowest quintile \( p < 0.001 \) (28). A similar trend was seen in the Quebec Cardiovascular Study. Among the ∼2000 subjects who were followed for 5 years, those in the highest quartile for fasting insulin had ∼8-fold elevations in their odds ratio for coronary heart disease, relative to the lowest quartile (29). These associations, however, do not necessarily prove a causal relationship between insulin resistance (or hyperinsulinemia) and atherosclerosis. The ability of the several surrogate indexes of insulin resistance to predict cardiovascular disease is under debate (Fig. 15, Fig. 16 and Fig. 17).

<table>
<thead>
<tr>
<th>Some degree of glucose intolerance</th>
<th>Hemostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired fasting glucose</td>
<td>Plasminogen activator inhibitor-1</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>Fibrinogen</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>Endothelial dysfunction</th>
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</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>Mononuclear cell adhesion</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Plasma concentration of cellular adhesion molecules</td>
</tr>
<tr>
<td>LDL-particle diameter</td>
<td>Plasma concentration of asymmetric dimethyl arginine</td>
</tr>
<tr>
<td>Postprandial lipemia</td>
<td>Endothelial-dependent vasodilatation</td>
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</table>

<table>
<thead>
<tr>
<th>Hemodynamic</th>
<th>Reproductive</th>
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<tbody>
<tr>
<td>Sympathetic nervous system activity</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>Renal sodium retention</td>
<td></td>
</tr>
</tbody>
</table>

| Blood pressure (50% of patients with hypertension are insulin resistant) |
| Renal uric acid concentration             | Reaven, Circulation 2003       |
| Renal uric acid clearance                 |                                |

Figure 14

The disorders associated with insulin resistance, together with endothelial dysfunction, are all likely to be part of the pathogenesis of atherosclerosis. In fact, insulin resistance might directly contribute to endothelial cell dysfunction and atherosclerosis. Activation of the NO pathway by insulin in the endothelial cell, which has beneficial antiatherogenic effects through NO-mediated vasodilation, may be impaired in individuals with insulin resistance (27). The Paris Prospective Study showed that men in the highest quintile of plasma insulin had a ∼2.5-fold higher relative risk for CHD mortality compared with those in the lowest quintile \( p < 0.001 \) (28). A similar trend was seen in the Quebec Cardiovascular Study. Among the ∼2000 subjects who were followed for 5 years, those in the highest quartile for fasting insulin had ∼8-fold elevations in their odds ratio for coronary heart disease, relative to the lowest quartile (29). These associations, however, do not necessarily prove a causal relationship between insulin resistance (or hyperinsulinemia) and atherosclerosis. The ability of the several surrogate indexes of insulin resistance to predict cardiovascular disease is under debate (Fig. 15, Fig. 16 and Fig. 17).
Figure 15

CHD Prevalence

Age-adjusted prevalence of metabolic syndrome in the U.S. population over 50 years of age

Alexander et al. NHANES study. Diabetes 2003; 52:1210
HOMA predicts cardiovascular disease

Figure 16

Bonora et al. Diabetes Care 2002; 25:1135
Hanley et al; Diabetes Care 2002; 25:1177-1184

Figure 17

References


27. Feener EP, King GL. Vascular dysfunction in diabetes mellitus. Lancet. 1997; 350(Suppl 1),S19-S113
