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Insulin resistance as an independent risk factor for cardiovascular disease: clinical assessment and therapy approaches

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ABSTRACT

Insulin resistance of glucose metabolism is a typical feature of type 2 diabetes mellitus but it can be observed in several other common clinical conditions and also in many apparently healthy subjects. Overall, as many as 30-40% of subjects from the general population are insulin resistant. The euglycemic hyperinsulinemic clamp is the gold standard technique in the assessment of insulin resistance but it cannot be used in epidemiological and clinical settings. In these situations a feasible surrogate approach might be the Homeostasis Model Assessment, based upon the measurement of fasting glucose and insulin concentrations. Insulin possesses a number of biological effects that can be regarded as anti-atherogenic. These effects are blunted in insulin resistant states, predisposing to the development and the progression of atherosclerosis. Yet, insulin resistance is strongly related to several classic cardiovascular risk factors such as hyperglycemia, obesity, high triglycerides, low HDL cholesterol, hypertension and microalbuminuria. Finally, insulin resistance is related to many non-traditional risk factors like PAI-1, fibrinogen, CRP and other markers of inflammation. Therefore, insulin resistance is the common denominator of a constellation of risk factors and in most cases it plays a causal role: it is a pathogenic factor of several risk factors. In a number of cross-sectional and longitudinal studies insulin resistance of glucose metabolism was able to predict prevalent or incident cardiovascular disease also independently of classic and, in some studies, also of non-traditional risk factors. Insulin sensitizing strategies based upon changes in life style (e.g., reducing caloric intake and/or increasing physical activity) in non-diabetic subjects as well as the use of insulin sensitizers like metformin or thiazolidinediones in type 2 diabetic subjects yielded a prevention of cardiovascular disease. These data confirm the major role played by insulin resistance in cardiovascular disease and suggest that this common metabolic disorder should be effectively targeted in order to reduce cardiovascular risk.

Key Words: Insulin Resistance; Cardiovascular Disease; Risk Factors; Metformin; Thiazolidinediones.

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Acrónimos: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; FFA, free fatty acid; HOMA, Homeostatic Model Assessment; HOMA-IR, HOMA insulin resistance score; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL-6, interleukin- 6; IST, insulin suppression test; ITT, insulin tolerance test; IVGTT+MinMod, intravenous glucose tolerance test with the minimal model analysis; PAI-1, plasminogen activator inhibitor-1; TNF- α, tumor necrosis factor-α; UKPDS, UK Prospective Diabetes Study; VWF, von Willebrand Factor

EPIDEMIOLOGY OF INSULIN RESISTANCE

Insulin resistance is the experimental or clinical condition in which the hormone exerts a biological effect less than expected. It can be observed and measured in the whole body, an organ, an isolated tissue, or a cell culture. Insulin resistance of glucose metabolism is also a statistical predictor, a pathogenic factor and a biological hallmark of type 2 diabetes, where it can be found in more than 80% of subjects, but it can be observed in several other clinical conditions. As many as 80% of subjects with isolated hypertriglyceridemia and/or isolated low HDL cholesterol are insulin resistant, at least half of subjects with isolated overweight or obesity are insulin resistant, and about 20% of subjects with isolated high blood pressure or isolated hyperuricemia are insulin resistant[1]. Yet, there are other common or less common clinical conditions featured by insulin resistance, e.g. polycystic ovary syndrome or non-alcoholic fatty liver disease[2,3]. Moreover, also 20-25% of apparently healthy individuals, depending upon the diagnostic criteria and the methods used, have insulin resistance[1,4].

If we speculate about the epidemiology of insulin resistance of glucose metabolism, we can reasonably estimate that subjects affected are 30 to 40%, i.e. a large proportion of the general population. Insulin resistance, in other words, is not a problem confined to diabetes, but is a sort of mass phenomenon. In fact, if we consider how diffuse are diabetes and the prediabetic conditions (impaired fasting glucose, IFG, and impaired glucose tolerance, IGT), overweight and obesity, dyslipidemia, hypertension and hyperuricemia, and if we consider that many other metabolic and non-metabolic, endocrine and non-endocrine diseases and that also apparently healthy subjects are quite often featured by insulin resistance, we can conclude that hundreds of millions people and probably billions of people have insulin resistance throughout the world.

CLINICAL ASSESSMENT OF INSULIN RESISTANCE

The above mentioned conclusion certainly applies to insulin resistance of glucose metabolism, i.e. the abnormal biological effect of insulin which was the subject of countless researches, and the one which is less complicated to be detected. Nevertheless, as discussed below, also the assessment of insulin resistance of glucose metabolism is not easy, especially in the clinical setting.

The hyperinsulinemic euglycemic clamp is the gold standard technique in the assessment of insulin resistance. Subjects to be examined undergo a prime-constant i.v. infusion of insulin to raise the hormone to a steady state level of 50-100 μU/ml which is maintained for at least 2 hours, while plasma glucose is prevented to fall by a variable i.v. glucose infusion which keeps (or "clamps") glucose at euglycemia. In diabetic patients plasma glucose can be clamped at its initial value ("isoglycemic clamp") or can be let to drop until euglycemia is reached and than it is clamped at such level. The overall amount of glucose infused during the infusion of insulin equals glucose metabolized by the body for the effect of the hormone and gauges whole body insulin sensitivity. It represents both the suppression of endogenous glucose production and the increase in glucose utilization in the insulin sensitive tissues (mainly the skeletal muscle)[5]. The method requires two pumps, a bed-side glucose analyzer and trained physicians and/or nurses. The proband (patient) must stay in a bed at the hospital for about 3 hours. Results are immediately available. The test is cumbersome, costly and time-expensive. It is, however, precise and accurate and is not based upon any kind of assumptions, it measures the amount of glucose metabolized (mg, μmol) in a given time (minute, hour) per kg body weight or m^2 surface area. The combined use of a glucose tracer (e.g., tritiated or deuterated glucose) allows the separate assessment of both hepatic and peripheral insulin sensitivity[6]. The additional use of indirect calorimetry generates information on oxidative and non-oxidative glucose disposal during insulin infusion[6].

Alternative methods in the assessment of insulin sensitivity are: a) the intravenous glucose tolerance test with the minimal model analysis of glucose and insulin kinetics (IVGTT+MinMod)[7]; b) the insulin suppression test (IST), based upon the triple i.v. infusion of glucose, insulin and somatostatin and the calculation of steady state plasma glucose[8]; c) the short insulin tolerance test (ITT), which measures the rate constant of glucose disappearance from plasma after i.v. insulin injection[9]. The IVGTT+MinMod is the most widely used among these three alternative tests because it also generates information on insulin secretion. The test, however, is less accurate in diabetic subjects in whom an i.v. bolus injection of tolbutamide or insulin during the test is necessary for appropriate modelling. Although IVGTT+MinMod, IST and ITT generate data on insulin sensitivity which are quite well correlated to those achieved with the gold standard (i.e., the clamp), they are not substantially less complex than the clamp and, therefore, cannot be used in epidemiology or in clinical practice.

In the epidemiological and the clinical setting the assessment of insulin sensitivity must necessarily rely on a single

blood sample. Upon the assumption that an homeostatic compensation does exist between impaired insulin sensitivity and beta-cell hypersecretion, the assessment of fasting plasma insulin was used in several studies as a surrogate measure of insulin sensitivity[10]. In fact, the lower is insulin sensitivity, the higher is insulin secretion and, therefore, plasma insulin. However, when beta-cell secretion is impaired, as in type 2 diabetes, this homeostatic compensation is disrupted or totally lost, and fasting plasma insulin is not as good in the estimate of insulin sensitivity as in nondiabetic subjects. In type 2 diabetes, and also in non-diabetic subjects, a better estimate can be achieved with the use of formulas or models based upon glucose and insulin levels in the fasting state and/or after oral glucose load[11]. The most popular of these approaches is the Homeostatic Model Assessment (HOMA)[12], which generates data on insulin sensitivity which are very well correlated to data achieved with the glucose clamp in both nondiabetic and diabetic subjects[13]. Moreover, the HOMA approach is able to predict the future development of diabetes as well as the glucose clamp does[14].

The HOMA has the virtue of simplicity in the assessment of insulin sensitivity and has good reproducibility within the same laboratory. However, it remains a surrogate method, which does not provide information on the amount of glucose metabolized during insulin exposure. It just allows a reliable categorization of subjects according to their insulin sensitivity. The major drawback of the HOMA approach is the poor reproducibility of plasma insulin measurement across laboratories[15]. This problem is a serious obstacle in the definition of a generalized threshold for hyperinsulinemia and of a standardized cut-off for HOMA insulin resistance score (HOMA-IR). At present, each laboratory should identify, based upon its own studies in healthy individuals, its range of normality for insulin and HOMA-IR and its cut-off for hyperinsulinemia and insulin resistance. This makes hard the use of HOMA in the estimate of insulin resistance in the clinical setting.

A simple approach in the clinical evaluation (in the estimate rather than in the assessment) of insulin resistance might be the identification of features typically associated with this metabolic disorder in the single individual. Many epidemiological studies have documented that type 2 diabetes and the prediabetic conditions, overweight/obesity, dyslipidemia (high triglycerides, low HDL cholesterol), hyperuricemia and hypertension are often associated with insulin resistance, especially when they cluster[1]. Therefore, the finding of three or more of these features in a given subject is a reasonable demonstration of the presence of insulin resistance[1]. This approach, as well as the finding of unquestionable hyperinsulinemia or high HOMA-IR, has a good specificity (up to 90%) but a poor sensivity (50-60%). In other words, all these approaches have few rates of false positives but, unfortunately, high rates of false negatives. Predictive equations based upon the use of simple clinical features were also developed but they do not provide a clear advantage[16].

ANTI-ATHEROGENIC EFFECTS OF INSULIN

When we speculate about the association of insulin resistance with cardiovascular disease, we should always remember that insulin has a wide spectrum of biological effects that go far beyond the well known hypoglycemic effect of the hormone. Insulin also impacts on lipids, amino acids, keton bodies, uric acid, cations, DNA, genes, and it modulates biological functions within the skeletal muscle, the adipose tissue, the liver, but also within the heart, the vasculature, the kidney, the brain, the skin, the bone, the blood cells. Virtually, all cells are a target of insulin and, hence, all cells can be involved in insulin resistance. Insulin resistance, therefore, is not a matter only of glucose, but also of lipids and urate, blood pressure, coagulation and fibrinolysis, inflammation and endothelial function. In other words, insulin resistance impacts not only glucose metabolism, but also other aspects of human physiology and is thought to play a major role in the pathogenesis of several metabolic and non-metabolic abnormalities.

Interestingly, an array of insulin actions can be regarded as anti-atherogenic. It is well know that insulin modulates lipid metabolism in several ways, including the inhibition of triglycerides hydrolysis in the adipose tissue, the inhibition of apoprotein B-100 synthesis in the liver and the stimulation of lipoprotein lipase in the endothelium[17]. These effects have a strong impact on lipid profile. Moreover, insulin reduces platelet aggregation[18] and fibrinogen synthesis[19], possesses anti-inflammatory and anti-oxidant properties[20,21] and favorably influences the endothelial function and the physiology of the vascular wall[22,23]. If we assume that insulin resistance is not generally confined to glucose metabolism but extends to many, if not all, biological effects of the hormone, these anti-atherogenic effects of insulin would be blunted in insulin resistant states. In other words, if few or many of the potentially anti-atherogenic effects of the hormone are impaired due to insulin resistance, an accelerated atherosclerosis is expected to occur.

INSULIN RESISTANCE AND CLASSIC CARDIOVASCULAR RISK FACTORS

Insulin resistance of glucose metabolism is strongly related to several classic cardiovascular risk factors like hyperglycemia, obesity, high triglycerides, low HDL cholesterol, hypertension and microalbuminuria[24]. Most importantly, when the general population is stratified according to the number of abnormalities clustering in the same individual, the abnormalities being impaired glucose regulation, hypertension, dyslipidemia, obesity or central fat distribution, microalbuminuria, i.e. the features of the Metabolic Syndrome, insulin resistance increases across categories, and subjects with 4 to 5 abnormalities have the most severe insulin resistance[25]. These data, and also many other data of the literature, clearly indicate that insulin resistance adversely affects several classic cardiovascular risk factors and, hence, drives to cardiovascular disease. There is no doubt that insulin resistance is a risk factor of classic cardiovascular risk factors.

INSULIN RESISTANCE IS INDEPENDENTLY RELATED TO CVD

There is good evidence that insulin resistance can contribute to cardiovascular disease also independently of classic risk factors. Several cross-sectional studies documented that insulin resistance, as assessed by various techniques, is related to coronary, carotid or peripheral vascular disease in both nondiabetic and diabetic subjects, also independently of classic risk factors[26-28]. More recently, these findings were confirmed in longitudinal studies[29,30]. In diabetic subjects when we used the HOMA, we found that for 1 standard deviation increase in (log) HOMA-IR, the risk of developing a cardiovascular event was about 50% higher (OR 1.54, 1.14-2.12, $p < 0.001$)[31]. In the general population subjects in the top quartile of distribution of (log) HOMA-IR had a ~80% increase in the risk for CVD (OR 1.77, CI 1.03-3.02, $p = 0.038$), after adjusting for classic and non-traditional risk factors (Bonora, et al., unpublished data).

The question now is: Which are the actors playing in this shortcut? Or, which are the intermediate abnormalities linking insulin resistance and cardiovascular disease independently of classic risk factors?

INSULIN RESISTANCE AND NON-TRADITIONAL RISK FACTORS

Over the last few years a bulk of experimental and clinical evidence indicated that insulin resistance is related to many non-traditional risk factors. For example, when we compared the most insulin sensitive with the most insulin resistant subjects, i.e. those of the lower quartile vs. those of the upper quartile of HOMA-IR, from the Bruneck Study, we found that the latter had higher levels of circulating endothelial adhesion molecules, after adjusting for sex, age, BMI (or waist girth) and smoking[25]. These circulating adhesion molecules are a marker of endothelial dysfunction and existing atherosclerosis and predict clinical cardiovascular events. The most insulin resistant subjects, i.e. those in the upper quartile of HOMA, had further abnormalities: they had higher free fatty acid (FFA), urate, fibrinogen, ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leptin, and oxidized LDL, and lower adiponectin after adjusting for possible confounders[25]. We also know from other studies that these patients have abnormalities in the fibrinolytic system, like higher plasminogen activator inhibitor-1 (PAI-1) concentration in blood[32] as well as higher coagulation factor VII, white blood cell count, sialic acid, alfa-1 acid glycoprotein, interleukin- 6 (IL-6), tumor necrosis factor-α (TNF-α), von Willebrand Factor (vWF). Several of these abnormalities document a state of chronic mild inflammation. Interestingly, many of these parameters are risk factors of cardiovascular disease. Overall, these data suggest that insulin resistance can adversely affect several non-classic cardiovascular risk factors and, hence, drives to cardiovascular disease. There is no doubt that insulin resistance is a risk factor of non-classic CVD risk factors.

INSULIN RESISTANCE IS A COMMON DENOMINATOR OF SEVERAL RISK FACTORS

In a wide angle perspective we might consider insulin resistance as a common denominator and probably a central causal disorder affecting several metabolic parameters like glucose, lipids, urate but also adversely affecting blood pressure, fibrinolysis and coagulation, oxidative stress, endothelial function and inflammation. Many literature data, indeed, support the conclusion that insulin is causally related to many non-traditional risk factors[33-36].

Insulin resistance seems to be a gateway to several physiological derangements which ultimately impact on the arterial wall: it worsens the profile of risk because it increases glucose, lipids and blood pressure, it favors a prothrombotic state through abnormalities in the coagulation and the fibrinolysis, it deteriorates the endothelial function, it promotes monocyte transmigration, LDL oxidation, foam cell formation, inflammatory molecules synthesis and release, vascular smooth cell proliferation and migration and plaque

formation and rupture. There is good experimental evidence that a bulk of adverse effects is promoted by insulin resistance in the arterial wall.

INTERVENTION STUDIES AND TRIALS

In order to corroborate the existence of a mechanistic link between insulin resistance and all of these abnormalities one should document that improving insulin resistance yields an amelioration of many of these disturbances. Accordingly, it was observed that changes in life-style resulting in weight loss and improved insulin sensitivity yield an amelioration of most of the abnormalities typically associated with insulin resistance[37]. As to drugs, insulin sensitizers like metformin and, to a greater extent, the thiazolidinediones, have several beneficial effects that go far beyond their hypoglycemic effect. These drugs do not only reduce glucose and HbA_{1c} in blood, but they also reduce FFA and triglycerides levels, increase HDL-cholesterol concentrations, reduce blood pressure, increase the size of LDL making these particle less susceptible to oxidation and less atherogenic, reduce PAI-1 and a number of markers of oxidative stress, inflammation and endothelial dysfunction[38-41]. In other words, these compounds have potentially favorable effects on several actors on the atherosclerotic scene.

The association between insulin resistance and cardiovascular disease is supported by many experimental studies, many clinical studies and many observational studies. The conclusive proof that this association is causal and not casual or without any mechanistic implication must come from intervention trials. Unfortunately, few intervention trial specifically addressed the issue of the effect of ameliorating insulin resistance on cardiovascular outcome. There are studies in progress but, few data are currently available. We have some evidence from the UKPDS. In this trial, intensive treatment with sulphonylureas and insulin did not significantly reduce the incidence of myocardial infarction as compared to conventional treatment in overweight patients, whereas intensive treatment with metformin, a drug capable to improve insulin sensitivity, yielded a significant reduction in the incidence of myocardial infarction[42]. In the only trial completed so far with a thiazolidinedione, pioglitazone was able to reduce the occurrence of cardiovascular disease in type 2 diabetes[43]. Accordingly, pioglitazone and rosiglitazone were able to prevent progression of carotid atherosclerosis and coronary restenosis in type 2 diabetes[44,45].

CONCLUSIONS

Several routes seem to link insulin resistance to cardiovascular disease, one is going through classic risk factors (e.g., diabetes, dyslipidemia and hypertension), another one is going through non-classic risk factors (e.g. coagulation and fibrinolytic abnormalities). The assessment of insulin resistance may help identifying subjects at high risk of cardiovascular disease. Insulin sensitizing strategies seem to be able to favorably interfere at different levels and to make these routes more difficult to go through. These strategies are based upon changes in life-style and the use of drugs like metformin and thiazolidinediones, alone or in combination.

CONSIDERACIONES PRÁCTICAS

- La resistencia a la insulina es una condición clínica anormal, de elevada prevalencia en la población, y se asocia con numerosos factores de riesgo cardiovascular clásicos y no clásicos.
- La determinación en la clínica de la resistencia a la insulina puede permitir la identificación de un grupo de pacientes con riesgo cardiovascular elevado.
- La reducción de la resistencia a la insulina mediante la modificación del estilo de vida y/o la utilización de fármacos insulin-sensibilizadores como la metformina y las glitazonas (solas o en combinación) puede mejorar el riesgo cardiovascular elevado de los pacientes con diabetes.

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