



## Insulin resistance: Is it time for primary prevention?

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### Abstract

Insulin resistance is a clinical condition characterized by a decrease in sensitivity and responsiveness to the metabolic actions of insulin, so that a given concentration of insulin produces a less-than-expected biological effect. As a result, higher levels of insulin are needed to maintain normal glucose tolerance. Hyperinsulinemia, indeed, is one of the principal characteristics of insulin resistance states. This feature is common in several pathologic conditions, such as type 2 diabetes, obesity, and dyslipidemia, and it is also a prominent component of hypertension, coronary heart disease, and atherosclerosis. The presence of endothelial dysfunction, related to insulin resistance, plays a key role in the development and progression of atherosclerosis in all of these disorders. Insulin resistance represents the earliest detectable abnormality in type 2 diabetes, and is one of the major underlying mechanisms of hypertension and cardiovascular diseases. Its early detection could be of great importance, in order to set a therapeutic attack and to counteract the higher risk of diabetes and cardiovascular diseases.

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### INTRODUCTION

Insulin resistance can be defined as a condition in which insulin's target organs are resistant to its action, so that higher concentrations of this hormone are needed to obtain a normal biological effect. Therefore, hyperinsulinemia is an obvious consequence of insulin resistance, which contributes to the development of endothelial dysfunction, playing a key role in the establishment and progression of atherosclerosis. Insulin resistance represents the pivotal mechanism underlying type 2 diabetes, hypertension and cardiovascular diseases. Although a great amount of literature shows the deleterious action of insulin resistance and hyperinsulinemia in increasing the cardiovascular risk, nowadays there are no guidelines for the treatment of insulin resistance, but its early detection should be of great importance, since a prompt and adequate therapeutic attack may counteract the higher risk of diabetes and cardiovascular diseases. In this review of the literature, we explain the principal mechanisms by which insulin contributes to cardiovascular homeostasis, the main correlations among insulin resistance, visceral obesity, diabetes and cardiovascular risk, and, finally, the possible therapeutic approaches actually available.

INSULIN AND CARDIOVASCULAR HOMEOSTASIS

Insulin is a polypeptide hormone implicated in several biological processes, whose action is mediated by a transmembrane tyrosine kinase receptor. The binding of insulin to its receptor in target tissues leads to the activation of complex insulin-signaling pathways, which regulate the transcription of target genes<sup>[1-3]</sup>. Two major signaling branches have been identified: the phosphoinositide 3-kinase (PI3K)-dependent pathways that mediate the metabolic actions of insulin, including the regulation of glucose metabolism in muscle, adipose and hepatic tissues, and the regulation of nitric oxide (NO) production from endothelium and vascular smooth muscle cells (VSMC)<sup>[4-7]</sup>, and the mitogen-activated protein kinase (MAPK)-dependent pathways that mediate the non-metabolic actions of insulin, including the mitogenic and proliferative effects, the secretion of endothelin-1 (ET-1) by endothelial cells, and the increased expression of adhesion molecules on the vascular endothelium<sup>[8,9]</sup>. Under normal conditions, both these insulin-signaling pathways contribute to cardiovascular homeostasis, regulating distinct biological functions: the first one (NO-dependent) causes vasodilation, a decrease in vascular resistance, an increase in blood flow, and stimulation of capillary recruitment, whereas the second one (ET-1-dependent) causes vasoconstriction, which contributes to the activation of the sympathetic nervous system induced by insulin, exerting a pro-hypertensive action, and accelerating atherosclerotic damage<sup>[10,11]</sup>. The effects on vascular homeostasis mainly affect the cardiovascular system and skeletal muscle, which, in turn, is an important target for the metabolic effects of insulin, stimulating glucose uptake and glycogen accumulation. While glucose accumulation is mediated by translocation of glucose channels to the sarcolemma, the stimulation of physiological cardiac growth and contractility are due to the augmented calcium influx and myofilament calcium sensitivity, resulting in an increase in myocardial work and oxygen consumption<sup>[12-14]</sup>. These observations suggest a tight association between hemodynamic and metabolic actions of the hormone.

In conditions of insulin resistance there is a specific impairment in metabolic PI3K-dependent signaling pathways, whereas other insulin-signaling branches, including non-metabolic MAPK-dependent pathways, are unaffected<sup>[15,16]</sup>. Compensatory hyperinsulinemia, that typically is associated with insulin resistance in order to maintain euglycemia, overstimulates unaffected MAPK-dependent pathways, leading to an imbalance between PI3K- and MAPK-dependent effects of insulin<sup>[17,18]</sup>. This results in an overproduction of vasoconstrictor mediators, such as ET-1, and in a reduction of NO synthesis, with a resultant vasoconstrictor effect, a key feature of endothelial dysfunction<sup>[8,19,20]</sup>. In addition, hyperinsulinemia may lead to the development of systemic hypertension, not only by increasing ET-1 secretion and sympathetic

Table 1 Pathologic changes associated with insulin resistance and compensatory hyperinsulinemia

Altered glucose metabolism:
Impaired fasting glucose
Impaired glucose tolerance
Diabetes
Dyslipidemia:
↑ Triglycerides
↓ HDL-C
↑ Small, dense LDL-particles
Endothelial dysfunction:
↑ Adhesion molecules
↓ Endothelial-dependent vasodilation
↓ NO and ↑ ET-1 production
Hypercoagulability:
↑ Plasminogen activator inhibitor-1
↑ Fibrinogen
Hemodynamic changes:
↑ Sympathetic nervous system activity
↑ Renal sodium retention
↑ Cardiac mass
VSMC hypertrophy
Chronic inflammation:
↑ C-reactive protein, TNF-α, IL-6, resistin, leptin
↓ Adiponectin
↑ Oxidative stress

HDL-C: High density lipoprotein-cholesterol; LDL: Low density lipoprotein; NO: Nitric oxide; ET-1: Endothelin-1; VSMC: Vascular smooth muscle cells; TNF-α: Tumor necrosis factor-α; IL: Interleukin.

tone, but also by inducing antinatriuretic effects, because it promotes renal sodium retention by enhancing distal tubular sodium reabsorption<sup>[21]</sup>. Thus, these alterations may contribute to reciprocal relationships between endothelial dysfunction and insulin resistance, typical of both metabolic and cardiovascular diseases<sup>[22]</sup>. Endothelial dysfunction contributes to impaired insulin action. This establishes a reverberating negative feedback cycle in which progressive endothelial dysfunction and disturbances in glucose and lipid metabolism develop from the insulin resistance (Table 1).

VISCERAL OBESITY AND INSULIN RESISTANCE

Visceral obesity is the major risk factor for insulin resistance, since it plays a crucial role in the pathogenesis of this condition. The excess abdominal adipose tissue releases large amounts of circulating free fatty acids (FFA), which substantially impair the insulin-signaling pathways in the main target organs. This alteration leads to widespread changes in glucose and lipid metabolism. Indeed, in the liver, FFA cause an increased production of glucose, triglycerides and very low density lipoprotein-cholesterol (LDL-C). Other associated metabolic abnormalities include a highly atherogenic plasma lipid profile, characterized by an increase in small and dense LDL-C, and a reduction in high density lipoprotein-cholesterol (HDL-C)<sup>[23,24]</sup>. Concomitant hepatic alterations include a reduction in glucose storage in the form

of glycogen, and an increase in lipid accumulation in the form of triglycerides. FFA also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. The high circulating levels of glucose and FFA cause an increase in oxidative stress, due to the production of reactive oxygen species (ROS) and the increased formation of advanced glycation end-products, an alteration in the local renin-angiotensin system, and an increase in adrenergic activation of VSMC, that may all act in concert to contribute to the development of endothelial dysfunction<sup>[25,26]</sup>.

In addition to the effects on insulin resistance determined by the high levels of FFA, adipose tissue has an essential role in establishing a chronic pro-inflammatory state. Adipose tissue is in fact an active endocrine-paracrine organ, since it produces adipocyte-derived hormones, such as leptin and adiponectin. Leptin is a key regulator of appetite, body weight and energy balance in the central nervous system, beside exerting, under healthy conditions, an NO-dependent endothelium-mediated vasodilatory effect<sup>[27]</sup>. In pathological conditions, such as in the presence of visceral obesity, there is an alteration in the effects of leptin, which are associated with a promotion of vascular inflammation, oxidative stress and VSMC hypertrophy. This evidence suggests that leptin may potentiate both pro-hypertensive and pro-atherogenic effects of insulin<sup>[28]</sup>. Adiponectin is an anti-inflammatory peptide whose circulating levels are positively correlated with insulin sensitivity. It enhances NO bioavailability and reduces ROS production in endothelial cells<sup>[29]</sup>. It seems that adiponectin may be protective against ischemia-reperfusion injury in the heart<sup>[30]</sup>. In obesity-correlated insulin resistance states the secretion of adiponectin is reduced. Its plasma levels are negatively correlated with insulin resistance, and they may represent a potentially useful clinical marker of insulin resistance. In obese patients with insulin resistance, adipose cells oversecrete several adipo-cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), resistin<sup>[31]</sup>, plasminogen activator inhibitor-1, and interleukin-6, which promote atherosclerosis, vascular inflammation, and endothelial dysfunction, and impair the effect of insulin and its secretion<sup>[32]</sup>. TNF- $\alpha$  stimulates the production of C-reactive protein, which is considered an important marker of systemic vascular inflammation, and whose plasma levels are correlated with increased risk of cardiovascular events<sup>[33]</sup>. All these observations suggest that insulin resistance creates a state of low-grade, chronic, systemic inflammation, which provides a fascinating and physiologically sound reading frame bringing together the metabolic, vascular and hemodynamic hallmarks of atherosclerotic disease and cardiovascular risk. The presence of this constellation of metabolic alterations characterizes the so-called metabolic syndrome<sup>[34]</sup>.

## INSULIN RESISTANCE, DIABETES AND CARDIOVASCULAR RISK

Insulin resistance, as noted above, is a state in which a

given insulin concentration produces a lower-than-expected biological effect on glucose levels. This condition is counterbalanced by a compensatory increase in insulin secretion by pancreatic  $\beta$  cells, in the attempt to maintain normal glucose tolerance. Insulin resistance is the earliest detectable abnormality in the natural history of type 2 diabetes, whose evolution involves defects in both insulin action (insulin resistance) and insulin secretion ( $\beta$  cell dysfunction). Specifically, several studies have conclusively demonstrated that hyperinsulinemia, which develops in response to insulin resistance, precedes, often by many years, the development of type 2 diabetes<sup>[35,36]</sup>. Therefore, the plasma insulin concentration can be considered as a widely accepted surrogate measure of insulin resistance. The direct "gold standard" technique for the evaluation of insulin resistance is the euglycemic-hyperinsulinemic clamp; however, this is an invasive procedure useful for physiological and proof-of-concept studies, but not a plausible tool for population screening. The homeostasis model assessment of insulin resistance index [ $\text{HOMA-IR} = \text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glycemia (mmol/L)} / 22.5$ ] can nowadays be considered the best candidate non invasive surrogate marker of insulin resistance, since it correlates well with the "gold standard" clamp-derived values<sup>[37-40]</sup>. HOMA-IR is easy to measure, repeatable and cheap, therefore representing a useful means to detect insulin resistance both in the context of everyday clinical practice and in wide-scale clinical trials.

Type 2 diabetes can be considered as a cardiovascular disease featuring high plasma glucose levels<sup>[41]</sup>. Indeed, most diabetic patients already show signs of cardiovascular disease upon diagnosis<sup>[42]</sup>; it is well recognized that diabetic patients without a history of myocardial infarction have a risk of myocardial infarction comparable to that of non diabetic subjects with previous coronary events<sup>[43]</sup>. This is the principal reason why, in type 2 diabetic patients, cardiovascular risk factors must be treated as aggressively as in non diabetic patients with prior cardiovascular events (myocardial infarction, stroke), according to secondary prevention guidelines. Based on these observations, the need for an early intervention to screen and treat insulin resistance before type 2 diabetes becomes manifest seems warranted and obvious. Identifying and treating this condition promptly could counteract inflammation, atherogenic dyslipidemia, endothelial dysfunction, and hypercoagulability, all features responsible for the greatly increased cardiovascular risk in patients with insulin resistance. In fact, many studies have shown that insulin resistance, as assessed by HOMA-IR, is an independent predictive factor of cardiovascular disease, and a 1 unit increase in the HOMA-IR value is associated with a 5.4% increase in the cardiovascular risk<sup>[44]</sup>. The San Antonio Heart Study clearly demonstrated that HOMA-IR was significantly and independently associated with the risk of cardiovascular events in Mexican-American and in white non-Hispanic men and women<sup>[44]</sup>. Similarly, in another population study, HOMA-IR was predictive of cardiovascular disease, even after correction for age, gender, smoking and LDL-C. The latter study showed a relative risk of the incidence of cardiovascular end-points of



1.49 in insulin-resistant subjects (95% confidence interval, 1.07-2.07)<sup>[45]</sup>. It has also been shown that about 50% of normotensive subjects with insulin resistance develop some degree of diastolic dysfunction of the left ventricle with a relevant increase of the risk for heart failure<sup>[46]</sup>. In addition, insulin resistance is highly prevalent among non diabetic patients with chronic heart failure and it is associated with reduced exercise capacity<sup>[47]</sup>. Other important evidence has been highlighted by the Study of Inherited Risk of Coronary Atherosclerosis, which showed that, among many metabolic and inflammatory biomarkers, leptin and HOMA-IR were strongly and independently associated with coronary artery calcifications<sup>[48]</sup>. Furthermore, Schelbert demonstrated that insulin resistance was also associated with functional abnormalities in coronary hemodynamics, and that the extent of these abnormalities was proportional to the severity of insulin resistance. In particular, coronary dysfunction initially seems limited to a progressive worsening of endothelium-mediated vasodilatation, progressing to a complete impairment of vasodilatation capacity, in relation to the severity of insulin resistance. This endothelial dysfunction linked to insulin resistance, even in the absence of coronary artery macrovascular lesions, can result in a failure to appropriately increase coronary flow and in a drive towards the development of atherosclerosis, both of which may induce myocardial ischemia<sup>[49]</sup>. On the same topic, another manuscript reported that insulin resistance was present in young subjects with early myocardial infarction, who had no known factors with a negative action on insulin sensitivity<sup>[50]</sup>. Both insulin resistance and metabolic syndrome have been proved to be strong and independent predictors of cardiovascular risk in a group of patients with angiographically documented coronary artery disease, during a follow-up of 2 years and 3 mo<sup>[51]</sup>.

In support of the thesis of this review, i.e. that insulin resistance should be considered a strong risk factor for cardiovascular disease, the results of the Bruneck population study are very interesting. This long observational study confirmed that insulin resistance as assessed by HOMA-IR was associated with a greater incidence of cardiovascular events in the general population, independently from other known cardiovascular risk factors. The authors of this study emphasized that treatment of insulin resistance should be considered an important target to reduce the risk of cardiovascular disease<sup>[52]</sup>. Recently it has been reported that patients with pre-diabetes had defects in myocardial perfusion and transient left ventricular dilatation as measured by technetium (99mTc) sestamibi SPECT scintigraphy on the exercise treadmill, and that these defects correlated with HOMA-IR and waist circumference, independently of glucose levels<sup>[53]</sup>. Another recent paper reported the results of a study on HOMA-IR and the risk of cardiovascular events in middle-aged non-diabetic Japanese men. In this study, 2548 non-diabetic men aged 35-59 years were followed up for 11 years. The results showed that increased HOMA-IR at baseline predicted subsequent cardiovascular events, and that this

association was independent of traditional cardiovascular risk factors and other relevant metabolic disorders<sup>[54]</sup>.

In a recent study published in *Stroke*, insulin resistance, measured by the Gutt index, has been shown to be associated with the risk of incident ischemic stroke in non diabetic older adults<sup>[55]</sup>.

In addition to the data on the pathologic impact of insulin resistance on the cardiovascular system, recent papers have reported that insulin resistance could also be involved in cognitive impairment and neurodegeneration, particularly in Alzheimer's disease (AD). Epidemiological studies had already reported correlations among several metabolic alterations, such as diabetes, dyslipidemia and hypertension, and the risk of AD, but more recent studies have highlighted insulin resistance as potentially contributing to the development of AD. The increased risk of AD was associated with reductions in cerebral glucose metabolic rate, as measured by fluorodeoxyglucose F18-positron emission tomography, and subtle cognitive impairments at the earliest stage of disease<sup>[56]</sup>. These data have been in part confirmed by the results of the Rotterdam study, which showed that the levels of insulin and the degree of insulin resistance were associated with a higher risk of AD within 3 years of baseline<sup>[57]</sup>.

## THERAPEUTIC APPROACHES

The delay in the detection and management of insulin-resistant patients leads inevitably to late diagnosis, often in the presence of overt diabetes and established vascular complications. Therefore, in order to effectively counteract the deleterious effects of early, chronic hyperinsulinemia, screening for insulin resistance should be suggested at least in high risk subjects, such as those with abdominal obesity, and in relatives of diabetics. Once insulin resistance is recognized, current therapeutic approaches mainly involve lifestyle modifications. However, due to poor compliance with weight-loss diets and increased physical activity, pharmacological treatment is often needed to address insulin resistance effectively in the long term. Indeed, the optimal drug therapy should aim at counteracting the underlying negative impact of insulin resistance on metabolism and the cardiovascular system. Biguanides and thiazolidinediones are two classes of oral antihyperglycemic agents currently used in type 2 diabetic patients, that can reduce insulin resistance. Specifically, the effects of biguanides on insulin resistance are most likely correlated with a reduction in plasma FFA concentration<sup>[58]</sup>; in addition, metformin, the principal biguanide drug used in pharmacotherapy worldwide, induces a reduction in hepatic glucose production, an improvement in glucose uptake by skeletal muscles and adipose tissues, and a reduction in caloric intake and appetite<sup>[59,60]</sup>. Moreover, metformin has been shown to reduce the incidence of diabetes in persons at high risk, albeit to a lesser extent when compared with lifestyle modification<sup>[61]</sup>. Studies have shown that metformin lowers fasting glucose and hemoglobin A1c, with beneficial effects on

**Table 2** Therapeutic approaches to insulin resistance

	<b>Metformin</b>	<b>Thiazolidinediones</b>	<b>Berberine</b>
Main mechanism of action:	Activation of AMPK	Activation of PPAR $\gamma$	Activation of AMPK Up-regulation of insulin receptor expression Inhibition of intestinal disaccharidases
Metabolic effects:	Reduction in plasma FFA concentration Reduction in blood glucose, hemoglobin A1c, triglycerides, total and LDL-C, body weight and fat mass	Reduction in the amount of circulating FFA and in the lipolysis Improvement of hepatic production of glucose and insulin sensitivity	Reduction in plasma FFA concentration Reduction of blood glucose, hemoglobin A1c, total and LDL-C, triglycerides, body weight and fat mass
Side effects:	Abdominal discomfort, diarrhea and anorexia, lactic acidosis	Increase in total, LDL-C levels and body weight, hepatotoxicity, cardiotoxicity	Constipation

LDL-C: Low density lipoprotein-cholesterol; FFA: Free fatty acids; AMPK: AMP-activated protein kinase; PPAR: Peroxisome proliferator-activated receptors.

plasma levels of triglycerides, total cholesterol (TC) and LDL-C<sup>[60,62]</sup>. Most common side effects are abdominal discomfort, diarrhea and anorexia, while lactic acidosis is the most serious, but rare, possible adverse effect<sup>[63]</sup>. Thiazolidinediones (TZD) exert their action through the activation of the peroxisome proliferator-activated receptor  $\gamma$ <sup>[64]</sup>. These receptors play an important role in the modulation of glucose metabolism, involving adipocyte differentiation, with a reduction in the amount of circulating FFA and lipolysis. As a result, hepatic production of glucose and insulin sensitivity are improved<sup>[65]</sup>. In addition, TZD inhibit the activation of nuclear factor- $\kappa$ B, which controls the expression of many genes involved in immune and inflammatory responses, resulting in an improved endothelium-dependent vasodilation through an increased production of NO from endothelial cells<sup>[66]</sup>. However, the use of TZD is related to numerous well recognized side effects. TZD increased TC and LDL-C levels as well as body weight<sup>[67]</sup>. Troglitazone has been withdrawn from the market because of its hepatotoxicity<sup>[68]</sup>, and a recent meta-analysis highlighted that rosiglitazone is associated with a statistically significant increase in myocardial infarction and an increased risk of death from cardiovascular causes<sup>[69]</sup>.

Another therapeutic option can be represented by the natural alkaloid berberine. Its effects on lipid and glucose metabolism have been demonstrated by several scientific clinical and experimental studies<sup>[70-72]</sup>. The principal mechanism responsible of its insulin sensitizing action is the upregulation of insulin receptor expression<sup>[73,74]</sup>. Berberine lowers blood glucose, hemoglobin A1c, TC, LDL-C and triglycerides, and reduces body weight and fat mass<sup>[75]</sup>. In addition, it seems to have beneficial effects on endothelial function<sup>[74]</sup>. Its pleiotropic effects on glucose and lipid metabolism make berberine a good candidate for the treatment of dyslipidemic insulin resistant subjects (Table 2).

In conclusion, early detection of insulin resistance through screening of at-risk subjects should be counseled by medical societies in order to deliver prompt treatment to improve insulin resistance and reduce hyperinsulinemia. Therefore, lifestyle interventions of diet and physical exercise initially, and, in the case of poor

outcomes, the addition of insulin-sensitizing agents should be applied to the identified subjects, in order to counteract the higher risk of diabetes and cardiovascular diseases. A large multicenter trial should be performed in order to demonstrate the beneficial effects of early screening and intervention in insulin resistance on cardiovascular events, though there would be several issues because of the need for a wide population and a very long term follow-up.

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