What is insulin resistance?

Gurushankar Govindarajan, Harvinder Gill, Michael Rovetto and James R. Sowers
University of Missouri School of Medicine, Departments of Internal Medicine and Medical Pharmocology and Physiology, and Harry S. Truman VA Medical Center, Columbia, MO, USA

Correspondence: James Sowers, Department of Internal Medicine, Division of Nephrology, MA410, DC043.00, One Hospital Dr., Columbia, MO 65212, USA.
E-mail: sowersj@health.missouri.edu

Abstract

Reduced insulin responses and subsequent compensatory elevated plasma insulin concentrations result in abnormal function in all body tissues and present clinically as serious cardiovascular, renal, and diabetic related diseases. Insulin resistance most frequently results from changes in post-insulin receptor signalling pathways although insulin receptor changes may occur, (eg, production of receptor antibodies). Insulin resistance is genetically linked but obesity and lack of exercise are causes. Insulin resistance precedes type 2 diabetes and is strongly associated with hypertension, the cardiometabolic syndrome and polycystic ovary disease. There are a number of markers of insulin resistance and its treatment includes lifestyle changes and drug therapy for components of the syndrome.
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Definition of insulin resistance

Insulin resistance is a state in which there are impaired biological and physiological responses to insulin in tissue. In its early stages, there is a compensatory increase in insulin concentrations. Although hyperinsulinemia may compensate for resistance to some biological actions of insulin, it may result in overexpression of actions in tissues that retain normal or minimally impaired sensitivity to insulin. This metabolic dysfunction leads to a cluster of abnormalities with serious clinical consequences – most importantly, cardiovascular disease (CVD), chronic kidney disease and type 2 diabetes.

Mechanism of insulin resistance

Insulin resistance can be caused by prereceptor, receptor, or postreceptor abnormalities [1]. Prereceptor causes include the presence of anti-insulin antibody and abnormal insulin (mutation). The receptor causes for insulin resistance include decreased number of receptors, structural modification of the insulin receptor, and the presence of insulin receptor-blocking antibody. Both prereceptor and receptor causes of insulin resistance occur infrequently; the most usual cause is postreceptor in nature and involves the postreceptor signaling pathway.

Insulin has many physiological effects, which can be divided into acute and chronic: the acute effects include those that regulate intermediary metabolism, and chronic effects include the growth and proliferative effects of insulin. These two different actions are possible because of activation of two different cascades of actions by insulin. One pathway transmits the insulin signal through insulin receptor substrate (IRS) proteins and phosphatidyl inositol 3-kinases (PI3-K) to a series of intracellular proteins (*Figure 1*). Activation of this pathway is crucial for transducing the actions of insulin/insulin like growth factor-1 (IGF-1) in cardiovascular tissue, in addition to conventional insulin-sensitive tissues [1]. PI3-K mediates the increases in nitric oxide, Na^+ pump, K^+ channel, and calcium (Ca^{2+}) myofilament sensitivity by increasing the trafficking and translocation of nitric oxide synthase and cation pump units, in addition to glucose transporters. The second pathway involves activation of the mitogen-activation protein kinase (MAPK) pathway*, which increases growth and mitogenic processes

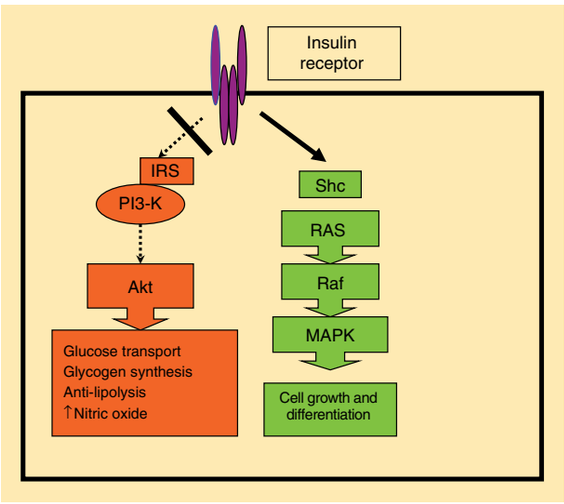

Figure 1. Insulin mediates its intracellular action through two different pathways. One, the phosphatidyl inositol 3-kinase/insulin receptor substrate (PI3-K/IRS) pathway through protein kinase B (Akt), regulates intermediary metabolism involved with glucose transport. The other pathway, through the adaptor protein (Shc), the guanine nucteotide binding protein (RAS) and serine-threonine kinase (Raf), and the mitogen-activated protein kinase (MAPK) cascade, regulates the growth and mitogenic pathway. In clinical insulin resistance, the resistance occurs in the PI3-K/IRS pathway.

[2,3]. In the vast majority of patients, the insulin resistance observed clinically is one that involves glucose metabolism through the PI3-K pathway (*Figure 2*). For this reason, the term 'insulin resistance', as used in clinical and experimental settings, is a state in which there is impaired glucose metabolism. Therefore, resistance to the actions of insulin and IGF-1 in these tissues occurs whenever there is reduced activation of PI3-K. In biological and physiological terms, however, it could apply to impaired response of the tissue to either of the two pathways.

Etiology of insulin resistance

Insulin resistance is postulated to have a genetic etiology, as it is observed to run in families. Other notable causes for insulin resistance include obesity and lack of exercise. Indeed, weight loss and exercise tend to reduce insulin resistance. Other causes of insulin resistance are listed in *Table I*.

Table I. Major causes of insulin resistance.

- Genetic abnormalities.
- Obesity and inactivity (leptins, cytokines, and excess free fatty acids may be involved).
- Counter-regulatory hormones.
- Immune-mediated (anti-insulin antibodies, anti-insulin receptor antibodies).
- Medications.
- Fetal malnutrition.
- Miscellaneous clinical conditions (eg, stress, chronic infections, pregnancy, starvation, cirrhosis, ketoacidosis, and uremia).

Table II. Prevalence of insulin resistance (IR) in certain clinical states. (From the Bruneck Study [5], with permission.)

Clinical state	Prevalance of IR (%)
Type 2 diabetes mellitus	84
Impaired glucose tolerance	66
Hypercholesterolemia	54
Low HDL and high triglyceridemia	85
Hypertension	58

HDL, high-density lipoprotein.

Prevalence of insulin resistance

The prevalence of insulin resistance in the general population varies with the criteria used for its definition. In certain studies it has been estimated that insulin resistance is prevalent in 30% of the adult population [4]. The prevalence of the condition is even greater in metabolic disease such as diabetes and the cardiometabolic syndrome [5]. *Table II*. lists the prevalence of insulin resistance in various disease entities. The increased prevalence of insulin resistance and the consequent cardiometabolic syndrome is being increasingly recognized in the USA, as obesity is becoming a major epidemic [6].

Insulin resistance and type 2 diabetes mellitus

Insulin resistance predates the onset of clinical type 2 diabetes mellitus by years. Most people have β-cell function that is adequate to fulfill normal tissue insulin requirements; the majority of these people also have considerable reserve, and could increase their insulin secretion considerably if necessary. However, a significant segment of the population exists that has limited reserve function. In this population, insulin resistance increases the insulin requirement of the tissue beyond the secretory capacity of the β cells. The recent surge in the incidence of diabetes mellitus worldwide can be attributed to an increased prevalence of insulin resistance in the general population as a result of the epidemic of obesity.

Insulin resistance and hypertension

It is estimated that about 25–47% of individuals with hypertension have insulin resistance [7]. Similarly, there is considerable evidence for an increased prevalence of hypertension in disease processes associated

Table III. Mechanisms of insulin resistance in hypertension.

Decreased nonoxidative glucose metabolism by skeletal muscle.
Post-insulin receptor defects:
- Decreased signaling through the PI3-K–Akt pathway.
- Decreased mobilization of GLUT-4 to the plasma membrane.
- Decreased insulin-mediated glucose transport.
- Decreased glycogen synthase activity.

Increased reactive oxygen species.
Altered skeletal muscle fiber type:
- Increased adipose tissue.
- Decreased insulin-sensitive slow twitch skeletal muscle fibers.

Decreased skeletal muscle blood flow with reduced delivery of insulin and glucose:
- Reduced generation of nitric oxide.
- Vascular rarefaction.

Vascular hypertrophy.
Increased vasoconstriction.

Akt, protein kinase B; GLUT-4, glucose transporter-4; PI3-K, phosphatidyl inositol 3-kinase. (from Reference [10], with permission).

with insulin resistance, such as type 2 diabetes mellitus [8]. Several mechanisms have been postulated for the high prevalence of insulin resistance in patients with essential hypertension (*Table III*) [9,10]. Some of the mechanisms suggested to underlie the coexistence of insulin resistance and hypertension include [11–17]:

- upregulation of the renin–angiotensin–aldosterone system;
- activation of the sympathetic nervous system;
- increased renal tubular sodium retention;
- increased intracellular calcium concentration;
- vascular smooth muscle cell proliferation and atherosclerosis;
- impaired nitric oxide metabolism in skeletal muscle.

Therapies targeted at insulin resistance, such as aerobic exercise or thiazolidinedione drugs, also result in a decrease in blood pressure [18,19].

Insulin resistance and the cardiometabolic syndrome

Metabolic dysfunction associated with insulin resistance leads to a cluster of abnormalities with serious clinical consequences – most importantly, CVD, type 2 diabetes mellitus, or both. This cluster of CVD and diabetic risk factors (which include central obesity, hypertension, dyslipidemia, microalbuminuria, and hypercoagulability) is known as the cardiometabolic syndrome. It was identified in 1988 by Reaven, who named the cluster 'syndrome X' [20]. Since Reaven, it has been given many other names; the more popular ones that are still applied to it include: the insulin resistance syndrome, the deadly quartet, obesity dyslipidemic syndrome, and the metabolic syndrome. This collection of risk factors increases the risk of CVD endpoints, such as stroke, congestive heart failure, chronic kidney disease, and overall mortality [6,10,21–23] (*Table IV*). The presence of even one or two of the risk factors multiplies the risk for both CHD and CVD [24]. The World Health Organization (*Table V*) [25] and the National Cholesterol Education Program (*Table VI*) [26] have produced diagnostic criteria for the identification of this syndrome among the general population (*Figure 2*).

Polycystic ovarian disease

Polycystic ovary syndrome (PCOS) is an exceptionally common disorder of premenopausal women, characterized by hyperandrogenism and chronic anovulation. The condition affects about 5–10% of women in the reproductive age group. Insulin resistance has proved to be a key factor in the pathogenesis of PCOS. The treatment of PCOS has, so far, been focused on treatment of the clinical signs and symptoms. Oral contraceptives have been the standard treatment. There is now a greater focus on the management of the metabolic consequences of PCOS, primarily through lifestyle intervention to achieve weight loss and increase physical activity. Insulin-sensitizing drugs such as metformin and thiazolidinediones have proved to be effective in the management of the

Table IV. The manifestations of metabolic syndrome that are associated with increased risk of cardiovascular disease.

- Impaired glucose tolerance
- Visceral obesity
- Microalbuminuria
- Chronic kidney disease
- Dyslipidemia
- Increased PAI/PA ratio
- Increased serum fibrinogen concentration
- Increased serum C-reactive proteins
- Increased uric acid concentration
- Increased production of interleukin-6
- Increased blood viscosity
- Increased systolic and pulse pressures
- Left ventricular hypertrophy
- Premature atherosclerosis
- Enhanced tissue RAAS
- Salt sensitivity
- Endothelial dysfunction

PAI/PA, plasminogen activator inhibitor/plasminogen activator; RAAS, renin–angiotensin–aldosterone system.

Table V. World Health Organization (WHO) clinical criteria for metabolic syndrome. (Data from Alberti et al. [26].)

Insulin resistance, identified by 1 of the following:
- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance or...
- For those with normal fasting glucose concentrations (< 110 mg/dL), glucose uptake below the lowest quartile for the background population under investigation under hyperinsulinemic, euglycemic conditions.

Plus any 2 of the following:
- Antihypertensive medication or high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) or both
- Plasma triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)
- Low HDL cholesterol: < 35 mg/dL (< 0.9 mmol/L) in men < 39 mg/dL (< 1.0 mmol/L) in women
- BMI > 30 kg/m^2 or waist : hip ratio > 0.9 in men, > 0.85 in women or both
- Urinary albumin excretion rate ≥ 20 μg/min or albumin : creatinine ratio ≥ 30 mg/g

BMI, body mass index; HDL, high-density lipoprotein. Similar to National Cholesterol Education Program–Adult Treatment Panel (ATP) III, the WHO consultation group also recognized cardiovascular disease as the primary outcome of this syndrome. However, demonstration of insulin resistance was required for diagnosis, which differs from the recent ATP III guidelines. In addition to insulin resistance, the presence of two other risk factors are sufficient for the diagnosis of cardiometabolic syndrome.

metabolic disturbances, anovulation, and hirsutism, and are now widely accepted therapies.

Laboratory studies to identify insulin resistance

The gold standard for the assessment of insulin resistance is the euglycemic hyperinsulinemic clamp test

Table VI. National Cholesterol Education Program–Adult Treatment Panel III clinical identification of the metabolic syndrome. (Adapted from McFarlane et al. [6], with permission.)

Risk factor	Cutoff value
Abdominal obesity, given as waist circumference	
Men	≥ 102 cm (≥ 40 inches)
Women	≥ 88 cm (≥ 35 inches)
Triglycerides	≥ 150 mg/dL
High-density lipoprotein	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/85 mm Hg
Fasting glucose	≥ 110 mg/dL

These risk factors include a combination of categorical and borderline risk factors that can be readily measured in clinical practice. When three of the five listed characteristics are present, a diagnosis of metabolic syndrome can be made.

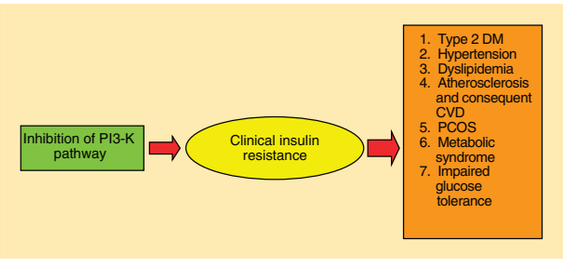

Figure 2. Clinical disease resulting from insulin resistance. Insulin resistance seen clinically is the result of impaired glucose metabolism arising out of inhibition of the phosphatidyl inositol 3-kinase/insulin receptor substrate (PI3-K/IRS) pathway. The consequences of insulin resistance depend partly on the background genetic makeup of the individual. CVD, cardiovascular disease; DM, diabetes mellitus; PCOS, polycystic ovary syndrome.

[27]. This technique involves the continuous intravenous administration of insulin and glucose over 3 hours, and the calculation of insulin sensitivity (the inverse of insulin resistance) by measuring the amount of glucose required to maintain normal glucose concentrations (euglycemia). However, the technique is impractical for routine clinical use, and therefore a number of surrogate indexes for insulin sensitivity or insulin resistance have been developed. The simplest and most commonly used marker in clinical practice is the homeostasis assessment (HOMA) model, which requires measurement only of the fasting plasma insulin and plasma glucose [28]. Using a patient's fasting blood values, the HOMA index for insulin resistance (HOMA-IR) can be calculated (*Table VII*):

$$\text{HOMA-IR} = (\text{fasting plasma insulin}\,(\mu\text{U/ml}) \times \text{fasting plasma glucose}\,(\text{mmol/L})/22.5$$

Similar to the HOMA index, there are other surrogate markers for insulin resistance such as log(HOMA) and the quantitative insulin-sensitivity check index (QUICKI). Chen et al [29] showed that log(HOMA) and QUICKI have an excellent linear correlation with the euglycemic hyperinsulinemic clamp test and are superior to many other surrogate indexes currently used.

Table VII. HOMA index for insulin resistance (HOMA-IR).

Group	Mean HOMA-IR
Normal individuals	2.1–2.7
Individuals with impaired glucose tolerance	4.3–5.2
Individuals with type 2 diabetes	8.3–9.5

Treatment of insulin resistance

Therapeutic lifestyle changes and drug treatment for individual components of insulin resistance are the current norm of clinical practice. Lifestyle changes – including a healthy diet and regular exercise – contribute to weight loss, improved blood glucose control, and reduced hypertension and other cardiovascular risk factors, and can even prevent the development of type 2 diabetes mellitus in persons with insulin resistance. When the therapeutic lifestyle changes are not sufficient, pharmacotherapy with an insulin sensitizer should be added. The thiazolidinediones are the only drugs approved specifically for the treatment of insulin resistance. Thiazolidinediones are novel drugs that specifically target insulin resistance. They are agonists for the nuclear transcription factor, peroxisome proliferator-activated receptor-γ, and reduce insulin resistance and increase the uptake of glucose into peripheral tissues, which results in decreased insulin concentrations; they are also involved in lipid metabolism.

Conclusion

In summary, the development of insulin resistance can have a profound impact upon a number of disease states and has led to the widespread prevalence of the cardiometabolic syndrome. As researchers are becoming able to identify the mechanism of insulin resistance, health care professionals will be able to counsel and treat their patients in a more effective manner. This will be of the utmost importance in the years to come, as the epidemic of diabetes continues to grow and afflict people all around the world. ■

* See glossary for definition of these terms.

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