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## Insulin resistance, does it exist? The current state of knowledge

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## **Abstract**

Insulin resistance is a growing concern worldwide, affecting millions of people and increasing the risk of various metabolic disorders, including type 2 diabetes, cardiovascular diseases, and fatty liver disease. This paper aims to display the symptoms of insulin resistance and the importance of early detection through various diagnostic tests such as fasting insulin levels, oral glucose tolerance tests, and HOMA-IR scores. Despite the high prevalence of insulin resistance, there is currently no known cure for this condition as it is not a disease in itself. However, lifestyle modifications, including exercise and dietary changes, can effectively manage and prevent the progression of insulin resistance and its associated complications. This study emphasizes the importance of raising awareness about insulin resistance and its adverse effects on individuals' health and the healthcare system's burden. Early detection and management of insulin resistance can significantly reduce the risk of developing metabolic disorders and prevent serious health complications.

Keywords: insulin resistance, sugar metabolism

## **Introduction**

Insulin resistance has been the subject of scientific investigation since the 1960s. Insulin resistance was initially detected in people with diabetes, and it was formerly described as requiring more than 200 units of insulin per day. [1]. However, due to rising awareness of the need of managing obesity and overweight concerns, there has been an increase in interest in this condition in recent years. Insulin resistance is a state of metabolism in which cells become insensitive to insulin, resulting in glucose buildup in the circulation [2]. It is critical to understand that insulin resistance is a condition, that can lead to the development of a variety of health issues, including type 2 diabetes and cardiovascular disease. Despite being a recognizable condition, insulin resistance remains a significant public health concern. The negative health effects of insulin resistance can lead to a significant strain on healthcare systems. As the number of persons affected by insulin resistance increases, so does the risk of chronic illnesses and the necessity for medical interventions. This might result in higher healthcare expenses [3]. The current global obesity epidemic is becoming increasingly prevalent, affecting a large number of individuals worldwide [4]. Therefore, understanding the underlying mechanisms and potential treatments for insulin resistance is crucial for the development of effective preventative and therapeutic interventions. In this study, we will review the currently funded studies on insulin resistance, including its etiology, diagnostic

criteria, symptoms, and related health consequences. We will also go through different therapies and techniques for managing and preventing insulin resistance. By giving a comprehensive review of this important issue, we want to contribute to continuing efforts to reduce the burden of insulin resistance and its accompanying health concerns.

### **Current state of knowledge**

From the clinical perspective, insulin resistance (IR) is a condition in which the body requires more insulin than usual to manage glucose levels in circulation. Pancreatic beta cells release this extra insulin. In essence, IR is a chronic and possibly reversible condition of decreased insulin responsiveness in major metabolic target tissues such as adipose tissue, liver, and skeletal muscle. As a result, the body experiences prolonged hyperinsulinemia. Hyperinsulinemia (hyperinsulinism) is a condition caused by insulin resistance that is defined by increased insulin levels in the bloodstream. Hypoglycemia is caused by an excess of insulin in the bloodstream. It occurs when the pancreas is prompted to release an excessive amount of insulin and the tissues become resistant to its effects. [5]. Insulin resistance (IR) is most usually induced by a considerable overflow of cells with excess energy reserves, which is produced by the accumulation of fatty tissue within them. This triggers the stage for a series of actions that limit future glucose and fatty acid entry. One of these mechanisms involves the creation of triglyceride breakdown products such as diacylglycerols, while another involves a reduction in the number of insulin receptors [6]. Other intracellular factors, such as mitochondrial dysfunction and degradation, as well as endoplasmic reticulum stress, may be involved in the pathogenesis of IR, but the precise pathomechanism is unclear. The precise origins of insulin resistance are unknown, although they are thought to encompass a complex interaction of variables at multiple levels, ranging from proteins and cells to organs and systems. At the cellular level, insulin resistance is thought to involve defects in insulin signaling pathways, which can interfere with the ability of cells to take up glucose from the bloodstream. This can be caused by various factors, including inflammation, oxidative stress, and the accumulation of certain fats in cells. On a broader level, insulin resistance is also influenced by genetic and environmental factors, such as family history, ethnicity, diet, and physical activity levels. A high-fat diet, as well as an excessive calorie intake, can all contribute to the development of insulin resistance. Insulin resistance has been linked to several medical disorders, including obesity, polycystic ovarian syndrome (PCOS), and sleep apnea. These diseases can aggravate insulin resistance and raise the chance of developing type 2 diabetes and other health problems. [7]. It's important to note that insulin resistance (IR) is not a disease. It does not have an International Classification of Diseases (ICD) code, no criteria for diagnosis or recovery, and

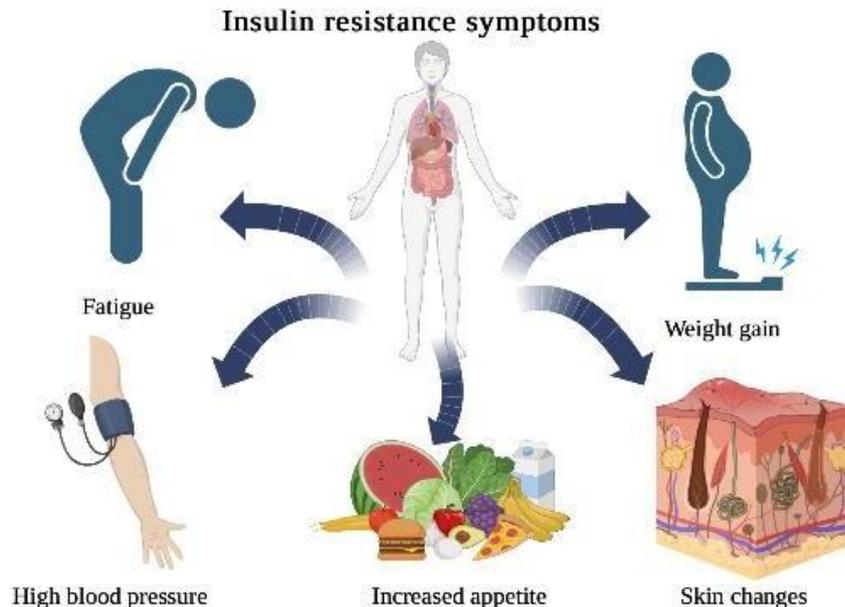
no drugs are recommended for treatment [8]. IR can be thought of as a defense mechanism that is induced as a reaction to significantly increased intracellular nutrient accumulation. If simultaneous hyperinsulinemia does not overcome tissue IR to maintain normoglycemia, the reduction in glucose and fatty acid intake into cells caused by IR may allow recovery to an energetically balanced condition. Insulin's physiological activity is not confined to glucose metabolism; it also facilitates the passage of fatty acids into cells and inhibits lipolysis (fat breakdown), which could end up in a rise in fat accumulation [9]. As a result, IR occurs, but it is not a disease, but rather a functional issue that results from the body's mechanisms of adaptation that minimize the input of glucose into cells by enhancing intracellular energy storage in the form of triglycerides. Fasting hyperinsulinemia, which is produced secondarily to maintain normoglycemia, is a detectable sign of these alterations.

### **Insulin resistance symptoms**

Insulin resistance symptoms might be difficult to detect since they are generally humble. These may include:

- Increased appetite - People who have insulin resistance frequently have high food desires and have difficulties managing their appetite [10].
- Weight gain - Insulin resistance frequently contributes to increased fat accumulation, which may lead to weight gain [11].
- Fatigue - As insulin resistance increases, cells discontinue taking up glucose and the body begins to utilize fat as a source of energy, resulting in exhaustion. Abnormal blood glucose levels - individuals with insulin resistance frequently have abnormal blood sugar levels, such as elevated fasting or post-meal glucose levels [12].
- High blood pressure - insulin resistance can induce excessive constriction of blood vessels, resulting in increased blood pressure [13].
- Skin changes - Insulin resistance may trigger darker skin regions on the neck area, groin, armpits, and other regions [14].

It is crucial to keep in mind that only certain individuals with insulin resistance will encounter these symptoms and other people may not have signs at all.



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Scheme 1. Insulin resistance Symptoms. Scheme was created using BioRender.

### **Insulin level**

It should be pointed out that fasting-state reference values for blood insulin concentration have only recently been established and range from 3 to 25 IU/ml. Different cut-off levels, even as high as 10 IU/ml, may be used in studies that assess risk or evaluate therapy efficacy. Fasting insulin levels in insulin resistance can either be increased or remain within the normal range. Individuals with insulin resistance may struggle to maintain a normal blood sugar level despite their pancreas releasing more insulin. As a result, the pancreas may overwork, resulting in tiredness and decreased insulin production later in this condition. In other words, depending just on fasting insulin levels to detect insulin resistance may be insufficient. [15]. Due to physiological variations in the release of insulin, reference values for postprandial insulin levels, including conventional oral glucose tolerance tests (OGTT), have not been established [16]. It is generally acknowledged that the amount of insulin released during the postprandial time should be adequate to safely avoid hyperglycemia, but this relies on multiple variables such as food composition (carbohydrate-rich meals demand more insulin secretion than fat-rich meals), emotional state (stress triggers an increase in cortisol and adrenaline), body weight and

physical activity [17]. Because there are no reference values, there is no point to monitor insulin levels during an OGTT test, and these results should not impact clinical choices.

## **OGTT**

The oral glucose tolerance test (OGTT) is a diagnostic examination used to determine how efficiently the body regulates glucose levels in the blood. This test involves monitoring blood glucose levels both before and after drinking a 75g glucose solution (120 minutes). OGTT is commonly used to diagnose diabetes and pre-diabetes stages. The use of OGTT to measure blood glucose levels is approved for the diagnosis of carbohydrate metabolism disorders. Despite it is relatively unusual for some people to test insulin levels during the OGTT, this approach is deemed inappropriate. As previously stated, the OGTT is not a diagnostic tool for insulin resistance, and interpreting insulin levels during the OGTT might be deceptive [18]. This is because the release of insulin and glucose metabolism are separate systems, and modifications in the amount of insulin can occur in reaction to a variety of stimuli other than glucose levels. This inaccuracy is due to a misunderstanding of how the levels of blood glucose are controlled and how insulin levels vary in reaction to consuming 75g of glucose in just a few minutes [19].

## **HOMA-IR**

The HOMA-IR index cannot be ignored when discussing insulin resistance. HOMA-IR stands for Homeostasis Model Assessment of Insulin Resistance. HOMA-IR is a mathematical model that represents the interaction between fasting glucose and insulin levels in the blood. It is determined by multiplying fasting insulin concentration (in IU/ml) by fasting glucose concentration (in mmol/l) and dividing by 22.5 [20]. HOMA-IR was not intended for use in regular clinical practice and has never been verified as a clinical measure for diagnostic or therapeutic choices [21]. There are no established standards for it, and several authors cite HOMA-IR threshold values for identifying insulin resistance ranging from 2-4 since different values have been employed in various studies to classify groups of patients undergoing therapies or surveillance. While HOMA IR is a popular and simple technique for measuring insulin resistance, it has certain limitations. HOMA IR only evaluates fasting insulin and glucose levels, which means it does not account for variations in insulin and glucose levels over the day. This might be a disadvantage because insulin resistance varies based on the time of day and after meals. In several cases, HOMA IR may not adequately measure insulin resistance: The HOMA IR model assumes that everyone's glucose-insulin connection is the same.

However, this is not always the case, since numerous factors, including genetics, food, physical activity, and other health issues, can impact insulin resistance. Other variables that may contribute to insulin resistance are not taken into consideration by HOMA IR: While insulin resistance is a role in type 2 diabetes and other metabolic problems, it is not the sole one. Inflammation, oxidative stress, and obesity may all play a role in the development of insulin resistance. [22].

### **Consequences of insulin resistance**

Insulin resistance can have major health repercussions over time. High insulin levels in the blood can alter cell function and damage blood vessels, raising the risk of cardiovascular disorders such as atherosclerosis [23], coronary artery disease, and heart attack [24], strokes [25]. Furthermore, insulin resistance is frequently associated with the development of type 2 diabetes. The body is unable to adequately use insulin in this condition, resulting in a rise in blood glucose levels. Diabetes type 2 can cause major problems such as nerve damage, kidney damage, vision impairment, and heart disease [27]. Long-term insulin resistance raises the risk of non-alcoholic fatty liver disease (NAFLD), which is linked to obesity and metabolic diseases. NAFLD can cause severe liver damage and, in severe cases, liver cirrhosis and hepatocellular cancer [28]. Furthermore, insulin resistance can have a considerable influence on an individual's quality of life since it frequently necessitates significant lifestyle modifications, such as dietary changes, exercise habits, and medication management. These modifications can be difficult to execute and maintain, and they may need continuing assistance from healthcare providers and family members. The rising frequency of insulin resistance and accompanying health concerns, for example, can create a major strain on healthcare systems, both in terms of treatment costs and demand for healthcare services.

### **Is insulin resistance treatment possible?**

Considering insulin resistance (IR) does not constitute a disease, discussing drugs for IR is challenging. There are treatments that can reduce IR, such as metformin [29] and PPAR-receptor agonists (Pioglitazone and Rosiglitazone), however, these are truly diabetes medications, and one of their mechanisms of action is to enhance insulin sensitivity [30]. Clinical research and guidelines for these medications show that their goal is to normalize glucose levels and that providing them to persons with normal glucose levels, except for those with PCOS, does not give any health advantages. As a result, administering metformin to people

who don't have carbohydrate tolerance problems to lower insulinemia is a bad idea because there's no scientific proof that it works [31].

Unfortunately, regardless of our improving understanding of the regulation of sugar and the widely discussed issue of insulin resistance, the major approaches to treat this disease still come down to physical exercise and a carefully balanced diet [32]. Patients are seldom able to manage it on their own, necessitating the assistance of many experts like physicians, nutritionists, trainers, and even psychotherapists. Insulin resistance, as we all know, is a metabolic illness that affects an increasing number of people globally [33]. Although the reasons for this ailment are numerous, its progression is sadly driven by a lifestyle that is dominated by bad eating habits and a lack of physical activity. Despite having easy access to a variety of sources of information on healthy living, people suffering from insulin resistance frequently require the assistance of a professional to successfully manage their health state. They necessitate a comprehensive strategy that includes not only a healthy diet and frequent physical activity, but also regular blood sugar monitoring, the need for lifestyle modifications, and, in some cases, psychological assistance. This is why patients with insulin resistance require a team of professionals to assist and support them at every level of therapy and lifestyle adjustments. Doctors, nutritionists, trainers, and psychotherapists are just a few of the professionals that will assist patients in understanding the root reasons for their condition and developing effective treatment and preventative plans. Patients will have a better chance of success in combating insulin resistance, and their lives will become healthier and more fulfilling as a result [34]

## **Conclusion**

In conclusion, increasing public knowledge of insulin resistance and related metabolic illnesses is a beneficial step toward bettering people's health. We are becoming increasingly aware that a healthy diet and regular physical activity are critical in avoiding and treating chronic disorders. As a result, implementing preventative actions to postpone or even avert the beginning of insulin resistance-related disorders is worthwhile. Steps that may be done include increasing physical exercise, adjusting food habits, checking blood sugar levels, and visiting the doctor on a regular basis. Striving for health and changing one's lifestyle is a time-consuming and commitment-intensive process, but it has several health and well-being advantages. We encourage everyone to take preventative measures and care for their health in order to live a long and healthy life free of insulin resistance-related disorders.

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