Original Article

Insulin Resistance: Recent Approaches, Consequences And And Scope

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Doi: 10.47750/pnr.2022.13.S05.360

Abstract

In the developed world, where obesity and diabetes are epidemics, the role of insulin resistance and its consequences are becoming increasingly important. Understanding insulin's involvement in a wide range of physiological processes, as well as its actions at the molecular and cellular levels as well as throughout the body, has significant implications for most chronic diseases that are currently prevalent in Western populations.

Following a discussion of insulin resistance and its associated clinical manifestations, this review provides an overview of insulin's history, structure, synthesis, secretion, actions, and interactions. The physiological, environmental, and pharmacological influences on insulin action and insulin resistance, as well as the clinical syndromes associated with insulin resistance, are some of the specific areas of focus. Other areas of focus include the actions of insulin and manifestations of insulin resistance in particular organs and tissues.

We must consider the significant social shifts that have occurred over the past century in terms of physical activity, diet, work, socialization, and sleep patterns, despite our limited comprehension of the intricate biological mechanisms underlying insulin action and insulin resistance. Obesity, diabetes, and the co-morbidities that go along with them have become epidemics as a result of rapid globalization, urbanization, and industrialization. This is because inactivity and a lack of balance in one's diet reveal hidden genetic traits that can lead to obesity and diabetes.

A clinical condition known as insulin resistance is one in which an impaired biologic response is caused by either a normal or elevated insulin level. Specifically, insulin-stimulated glucose disposal is the biologic response that has received the most research, but the specific cellular mechanism that is responsible for it is unknown. However, insulin resistance is present for a significant amount of time prior to the onset of clinical hyperglycemia and the diagnosis of Type 2 diabetes. At this stage, insulin resistance appears to be strongly linked to a group of cardiovascular risk factors that put the person at increased risk for cardiovascular disease. The clinical insulin resistant state and an overview of insulin resistance will be discussed.

(2) INTRODUCTION:

An impaired biologic response to insulin stimulation of the target tissues—primarily the liver, muscle, and adipose tissue—is what is known as insulin resistance. A compensatory increase in beta-cell insulin production and hyperinsulinemia is caused by insulin resistance's impairment of glucose disposal. Hyperglycaemia, hypertension, dyslipidaemia, visceral adiposity, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombic state are some of the metabolic consequences of insulin resistance. Non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and metabolic syndrome are all possible outcomes of insulin resistance progression.[1], [2] [3]

Although genetic causes have also been identified, insulin resistance is primarily an acquired condition that is connected to excess body fat. Due to the lack of a widely accepted test for insulin resistance, the clinical definition of insulin resistance remains elusive.[4] [5] Clinically, the metabolic consequences of insulin resistance, which are described in metabolic syndrome and insulin resistance syndrome, are how insulin resistance is recognized.

(2.1) SCOPE OF THIS REVIEW:

An overview of insulin, its structure, history, synthesis, secretion, actions, and interactions will precede a discussion of insulin resistance and its clinical manifestations in this review. The physiological and pathological mechanisms and

contexts of insulin resistance, as well as the clinical laboratory assessment of it, will be discussed in this final section. This review will not be comprehensive due to the topic's breadth; rather, it will serve as a context and gather the various current understandings of this constantly developing field.

(3) HISTORY:

Professor Wilhelm Falta first proposed the idea that insulin resistance may be the underlying cause of diabetes mellitus type 2 in a 1931 publication in Vienna [6]. In 1936, Sir Harold Percival Himsworth of the University College Hospital Medical Centre in London confirmed that insulin resistance was a contributor. However, type 2 diabetes does not occur unless there is concurrent failure of compensatory insulin secretion. [7]

(4) ETIOLOGY:

There are three types of etiology for insulin resistance: acquired, inherited, and mixed. The acquired categories apply to the vast majority of people with insulin resistance.

1) ACQUIRED-

- Ageing
- Physical inactivity
- Nutritional imbalance
- Glucose Toxicity
- Increased sodium diet
- Medications(protease inhibitors and some exogenous insulins
- Excess dysfunctional adipose tissue

There are a number of unrelated genetic syndromes that are associated with insulin resistance in addition to the heritable components of the aforementioned etiologies of insulin resistance.

2) GENETICS-

- Myotonic dystrophy
- Werner syndrome
- Type-A insulin resistance: characterised by severe insulin resistance in the absence of anti-insulin antibodies; typically occurs before middle age
- Type-B insulin resistance: characterized by the development of anti-insulin antibodies; typically in middle age
- Alstom syndrome
- Rabson-Mendenhall syndrome

5) EPIDEMIOLOGY:

The prevalence of metabolic syndrome or insulin resistance syndrome is typically used to measure insulin resistance in epidemiologic studies. The National Cholesterol Education Program Adult Treatment Panel III national survey data indicate that insulin resistance syndrome is extremely prevalent, affecting approximately 24% of adults over the age of 20 in the United States (US).Despite the rapid rise in childhood obesity and type 2 diabetes, there is currently no consensus regarding the diagnostic criteria for insulin resistance in children. The type-A syndrome mostly affects younger people, while the type-B syndrome mostly affects older people. All races are affected by insulin resistance from a demographic perspective, but there is insufficient data to compare different racial groups.

6) PATHOPHYSIOLOGY:

Adipose tissue, the liver, and muscle are the three most common insulin-resistant tissues. It is hypothesized that immune-mediated inflammatory change and excessive free fatty acid deposition in muscle begin insulin resistance. [8] [9] Up to 70% of glucose disposal occurs in muscle. De novo lipogenesis (DNL) and circulating free fatty acids rise as a result of impaired muscle uptake of excess glucose, which further contributes to insulin resistance and ectopic fat deposition.

• ADIPOSE TISSUE

Researchers discovered that lipolysis is most insulin-sensitive using the hyperinsulinemia-euglycemic clamp technique. In insulin-resistant adipose tissue, particularly visceral adipose tissue, circulating free fatty acids rise when insulin fails to inhibit lipolysis. Insulin resistance is made worse by higher levels of circulating FFAs that have direct effects on metabolism in the liver and muscles.

• MUSCLE TISSUE

After intake of a caloric load and conversion to glucose, muscle is the primary site for glucose disposal, accounting for up to 70% of tissue glucose uptake. With excess calorie loads, glucose uptake by muscle exceeds capacity, and excess glucose returns to the liver where it triggers DNL. Increased DNL increases triglyceride and FFA production, causing ectopic fat deposition into the liver, muscle, and adipose tissue. As a result, insulin resistance increases as well as the production of

inflammatory markers. Additional factors influencing insulin resistance in muscle tissue include physical inactivity and genetic risk.

- **HEPATIC TISSUE**

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7) TREATMENT:

The fundamental component of insulin resistance treatment is lifestyle intervention. A combination of calorie restriction and lowering the amount of high-glycaemic-index carbohydrates should be part of the diet intervention [10] [11] [12].Physical activity improves both calorie expenditure and insulin sensitivity in muscle

T2DM is more likely to occur in those with insulin resistance. According to the Diabetes Prevention Program and its Outcomes Study (DPP & DPPOS), lifestyle modification is a significant and cost-effective means of preventing diabetes in adults at high risk.

1) Specific pharmacological intervention for blood glucose management

- ***Metformin***-This is considered first-line therapy for medication treatment of T2DM and is approved for use in polycystic ovary syndrome.

- ***Glycogen-like peptide one inhibiters***- By stimulating the pancreatic GLP-1 receptors, the GLP-1 receptor agonists increase insulin release and decrease glucagon secretion. Weight loss is linked to GLP-1 agonist use, which may lower IR.

- ***Thiazolidinediones***- It increase insulin sensitivity by reducing hepatic glucose output and increasing insulin-dependent glucose disposal in muscle and adipose tissue. Although they are effective, their use is restricted due to the associated cardiovascular risks of secondary weight gain and fluid retention**.**

8) PROGNOSIS:

The subset of the disease, the severity of the disease, the function of the pancreatic beta cells, the patient's heritable susceptibility to the secondary complications of insulin resistance, and each patient's response to the appropriate treatment all influence the prognosis of insulin resistance. [13]

Asymptomatic mild insulin resistance all the way up to catastrophic cardiovascular or cerebrovascular events with subsequent morbidity and mortality make up the spectrum of outcomes.

There is a treatment for the disease. Early diagnosis and treatment are made possible by heightened clinical awareness. More targeted, multifaceted treatments have been developed as a result of increased comprehension of the disease process. Insulin resistance can be reduced and associated complications prevented by persistent efforts to attain and maintain a healthy weight through improved dietary intake and increased physical activity. Preventative care can be more effective if it is recognized by laypeople on a more general level, with the goal of reducing the obesity epidemic and insulin resistance that comes with it.

9) MECHANISM OF INSULIN RESISTANCE:

The actions of insulin are influenced by the interaction of other hormones at the whole-body physiological level. Although insulin is the main hormone that drives metabolic processes in the fed state, growth hormone and IGF-1 work together; In order to prevent insulin-induced hypoglycaemia, growth hormone is secreted in response to insulin and other stimuli. Glucagon, glucocorticoids, and catecholamines are additional hormones that counter-regulate. In the fasting state, these hormones drive metabolic processes. Glycolysis, gluconeogenesis, and ketogenesis are all aided by glucagon.

The degree to which the relevant enzymes are phosphorylated or dephosphorylated is determined by the ratio of insulin to glucagon [14]. Lipolysis and glycogenolysis are aided by catecholamines. Glucocorticoids encourage lipolysis, gluconeogenesis, and muscle catabolism. These hormones may be secreted in excess in some situations, but this does not account for the majority of states that are insulin resistant.

Post-receptor defects in insulin signalling are thought to be the most common mechanism by which insulin resistance manifests itself at the cellular level. Although a number of insulin signalling defects have been discovered in experimental animals, their relevance to insulin resistance in humans is currently unknown. Downregulation, deficiencies, or genetic

polymorphisms in the tyrosine phosphorylation of the insulin receptor, IRS proteins, or PIP-3 kinase are potential mechanisms, as are dysfunctional GLUT 4 functions.[33]

PHYSIOLOGICAL INFLUENCES ON INSULIN RESISTANCE:

1) *EXCERSICE AND PHYSICAL ACTIVITY-*

- Since the remarkable observation made by Chauveu and Kaufman in 1887, "When a horse chews on hay, the concentration of glucose in the blood draining its masseter muscle significantly decreases," [15]
- Exercise has been shown to improve insulin sensitivity and have positive effects on insulin resistance in a large body of research.
- Large-scale randomised controlled clinical trials, such as the Diabetes Prevention Program [16] and the Finnish Prevention Study [17], demonstrate a 58% reduction in the progression of impaired glucose tolerance to type 2 diabetes by intensive lifestyle modification, which included a minimum of 20–30 minutes of exercise per day. Epidemiological studies, such as the US Physicians Health Study, have reported that lifelong regular physical activity significantly reduces the relative risk of type 2 diabetes [18] .Exercise training appears to increase insulin sensitivity by increasing post-receptor insulin signalling; [19] increased insulin-mediated glucose transport appears to be related to enhanced signal transduction at the level of IRS proteins and PI 3-kinase. [20] In addition to this insulin-dependent mechanism, enhanced glucose uptake into exercising muscles occurs through multiple insulin in-dependent mechanism [21]. Acute exercise increases GLUT 4 translocation to the sarcolemma membrane, whereas chronic exercise training increases Glut 4 mRNA expression.

2) *STRESS-*

- The catabolic stress of severe illness is typically accompanied by insulin resistance, which has an impact on both mortality and morbidity.
- Mechanisms include the effects of inflammatory cytokines and the activation of the hypothalamic-pituitary adrenal (HPA) axis, which raises counter-regulatory hormones significantly.[22]
- The latter hinder insulin receptor signalling in liver, adipose tissue, and skeletal muscle; Several important signal transduction pathways are impacted by intermediates like ganglioside GM3, MAP kinase, IkB kinase, and ceramides. The potential significance of chronic psychosocial stress in the development of the metabolic syndrome has recently been reviewed.[83] Important examples include the inhibition of insulin receptor kinase activity via serine phosphorylation of IRS-1, with downstream effects on PI-3 kinase and GLUT 4 translocation, as well as direct effects on PI-3 kinase, Akt/protein kinase B, and protein kinase C. [23]

3) *PREGNANCY-*

- Insulin resistance is a characteristic of normal pregnancy, peaking in the third trimester. Human placental lactogen, progesterone, oestradiol, and cortisol, which act as counter-regulatory hormones to insulin, are thought to have combined to cause this adaptive response, which diverts glucose and lipids to the developing foetus [24]. Both gestational diabetes mellitus and gestational hypertension are caused by an overabundance of the insulin resistance that normally occurs during pregnancy. [25]

4). *OBESITY-*

- By French endocrinologist Jean Vague in 1956, increased adipose tissue, particularly that in the upper body or "android" deposition, was first linked to diabetes and vascular disease. [26] Insulin resistance increases with increasing body mass index, waist circumference, and especially the waist-to-hip ratio. [27] These measurements reflect increased adiposity, particularly increased levels of visceral adipose tissue. Visceral adipose tissue is the intra-abdominal fat that surrounds the intestines and is similar to liver fat. The metabolic characteristics of visceral adipose tissue differ from those of subcutaneous fat. When it comes to the turnover of free fatty acids, it is more metabolically active; Omental pre-adipocytes have increased 11-hydroxysteroid dehydrogenase type 1 activity, which was initially thought to promote insulin resistance by the effects of locally produced active glucocorticoid, via conversion of cortisone to cortisol; however, the significance of these findings in vivo is debated. [35] The increased flux of free fatty acids promotes insulin resistance at a cellular level and increases hepatic VLDL production.

COMMAN CONDITION ASSOCIATED WITH INSULIN RESISTANCE:

1. ***HYPERTENSION;-*** Up to 50% of cases of essential hypertension have been linked to insulin resistance [28] . Blood pressure is strongly correlated with body weight. Given that 50% of essential hypertensives do not appear to have insulin resistance, there is some debate regarding the significance of insulin resistance in hypertension. Endothelial dysfunction caused by resistance to insulin-mediated nitric oxide formation is thought to be of clearer significance, but compensatory hyperinsulinemia, which results in increased sympathetic nervous system activity and renal sodium retention, has been proposed as a possible mechanism.

2. ***CANCER-*** Certain cancers, including colon, endometrial, and possibly pancreatic and renal-cell cancers122, as well as breast cancer, have been linked to insulin resistance and compensatory hyperinsulinemia.[3] In the case of colonic

cancer, it is hypothesized that insulin resistance causes hyperinsulinemia, with elevated IGF-1 levels encouraging the proliferation of intestinal epithelial cells; In addition to the mitogenic effects of insulin itself, the effects of insulin resistance on ovarian function and sex hormone metabolism, as well as low levels of SHBG potentially elevating bio-available hormone levels, may also contribute to carcinogenesis. [29] Alterations in NF- B and peroxisome proliferator activated receptor signalling may also influence colonocyte kinetics.

3. ***OSA-*** Most people think of OSA as a side effect of obesity caused by mechanical obstruction of the upper respiratory tract while sleeping. However, there is some evidence to suggest that OSA is a systemic condition related to insulin resistance.[3] However, the fragmentation and hyperarousal of the resulting sleep may promote insulin resistance through activation of the HPA axis [30]. Sympathetic nervous system hyperactivity has also been reported in OSA. [31] Treatment of OSA by nasal continuous positive airway pressure preferentially reduces visceral adipose tissue[32]. These studies do not rule out the possibility that OSA contributes to insulin

MEASUREMENT OF INSULIN RESISTANC:

The assessment of insulin resistance in the laboratory can be done in a number of different ways. Older radio-immunoassays that cross-react with proinsulin and have limited specificity have made it less reliable to measure insulin resistance in clinical settings over time. The current assays are more precise and specific. The reader is encouraged to consult Spain[33] for a comprehensive review of insulin assays because this review is too long. Surrogate markers of insulin action, inference from the relative concentrations of glucose and insulin, or direct examination of insulin-mediated glucose uptake in the basal or post-stimulated state are all methods for measuring insulin resistance.

1. *RESEARCH METHOD-*

Due to their complexity and invasiveness, the most widely used methods for measuring insulin resistance are restricted to research settings. Under controlled conditions, the clamp studies specifically measure insulin-mediated glucose uptake. These include the hyperinsulinemia clamp and the euglycemic clamp, both of which are regarded as the gold standard. The insulin sensitivity test and the short insulin tolerance test are less invasive. The Homeostasis Assessment Model (HOMA) [34] , the Quantitative Insulin Sensitivity Check Index (QUICKI), the Continuous Infusion of Glucose with Model Assessment (CIGMA), the Frequently Sampled Intravenous Glucose Tolerance Test, and minimal modelling are examples of less direct methods for measuring insulin resistance. These strategies have recently been examined. [35]

2. *FUNCTIONAL MEASURES OF INSULIN RESISTANCE-*

Patients who are insulin resistant can also be identified using functional insulin resistance markers. By examining insulin concentration, plasma triglyceride concentration, and ratio of triglyceride to high-density lipoprotein cholesterol concentration, McLoughlin et al. were able to identify insulin resistant individuals from an overweight and obese cohort. They were able to diagnose the metabolic syndrome with a level of sensitivity and specificity that was comparable to that of the Adult Treatment Panel III by employing cut points of 109 pmol/L (16 mIU/L) for insulin, 1.47 mmol/L for triglyceride, and 1.8 mmol/L for the ratio of triglyceride to high-density
lipoprotein cholesterol. [36]

CONCUSIONS:

The significance of this topic as well as the medical and scientific interest in it have not diminished over the past century or more. Instead, latent genetic predispositions have been exposed by rapid globalization, urbanization, and industrialization, resulting in epidemics of obesity, diabetes, and the co-morbidities that go along with them. The mechanisms of biology are intricate, complicated, and only partially understood. However, if we take a step back, we might need to think about the significant social shifts that have taken place over the course of the past century in terms of work, diet, socialization, and sleep patterns. In addition to deciphering the genetic and mechanistic factors, creative adaptation of contemporary lifestyles to our genetic makeup and physiological requirements may present a greater challenge**.**

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