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Insulin Resistance: A Review

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Abstract
Insulin is a peptide hormone produced by the islet cells of the pancreas that has multifarious effects on body metabolism. Insulin resistance is a prevalent medical condition that accompanies type 2 diabetes, obesity, hypertension, metabolic syndrome and polycystic ovarian disease. It is a state in which higher than normal concentrations of insulin are needed for normal responses, leading directly to hyperinsulinaemia and impairment in some of its action. Its pathogenesis is yet not fully understood and that has restricted the treatment of type 2 diabetes and associated conditions. This review examines insulin resistance from the mode of action of insulin to its causes and consequences highlighting the recent findings with a view to making the condition better understood. Literature search was conducted from 1973 to date and 250 publications were reviewed. The mechanism of action of insulin is important in the understanding of insulin resistance. Changes in the downstream events following insulin- receptor interaction may play significant roles in the pathogenesis of insulin resistance. Currently, the roles of counter-action hormones including adipokines are fairly understood. More research is needed in the downstream events of insulin- receptor interaction to elucidate the pathogenesis of insulin resistance. This will change the current perception and practice in the treatment of type 2 diabetes and metabolic syndrome.

Keywords. *Insulin resistence (IR); hyperinsulinaemia, obesity, type 2 diabetes, impaired glucose tolerance, IR Index; hormone action.*

Introduction
Insulin resistance (IR) is a common medical issue that goes hand-in-hand with polycystic ovarian disease (PCOD), type 2 diabetes (T2D), obesity, hypertension, and metabolic syndrome (MetS) (1-2). Despite playing a significant role in the etiology of T2D and the metabolic syndrome, the processes behind IR are still poorly understood. It is a complicated metabolic condition with a pathogenesis that is interwoven. The insufficient knowledge of IR has limited the therapy of T2D. A deeper comprehension of IR processes is necessary to change diabetes from a deadly diagnosis to a chronic condition that can be treated medically. New pharmaceutical targets for the treatment of the metabolic syndrome and T2D will become apparent as a result of better understanding of the molecular/biochemical abnormalities responsible for IR. This review examines the IR phenomena with the aim to highlight aspects of IR needing attention for better understanding which will facilitate the management T2D.

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Definitions

Insulin is a peptide hormone produced by the islet cells of the pancreas. It is synthesized as pre-pro-hormone with a molecular weight of 11.5KD. A leader sequence (23- amino acids) directs the molecule into the cisternae of the endoplasmic reticulum before it is removed leaving a 9KD pro-insulin molecule made up of three polypeptide chains, A, B and a C (connecting) peptide and contains two inter- and one intra- disulphide bridges. The resulting pro-insulin molecule undergoes a series of genetic changes that result in the formation and eventual secretion of equimolar amounts of 51 amino acid insulin (A & B) and the C- peptide chains.

Insulin is now believed to be produced not only by the β cells of the pancreas but also by certain neurons of the central nervous system though in minute quantities (3).

In normal subjects, the principal stimulus for insulin secretion is the concentration of blood glucose that gets to the pancreas (4). Amino acids, beta adrenergic agonists, example, adrenaline; excessive levels of growth hormone, cortisol and sex hormones, stimulate and enhance insulin secretion (4).

Popular definitions of IR are with reference to the effects of insulin deficiency on glucose metabolism to cause diabetes. Recently there has been a shift from this traditional "glucocentric" view to an increasingly "lipocentric" viewpoint. Lipids accumulate within myocytes and hepatocytes in IR (5). IR may result from the disruption of different molecular pathways of insulin actions in target tissues (6). In IR, cells of the body do not respond normally to insulin, (7). A rise in plasma glucose levels usually leads to increased insulin secretion and circulating insulin levels. This causes the transfer of plasma glucose into peripheral tissues and inhibits hepatic gluconeogenesis. When this is defective, an individual is said to have IR (6, 8). In such individual, increased insulin secretion does not result in transfer of glucose into peripheral tissue and hepatic gluconeogenesis is not hindered. The phenomenon of IR was first described in 1936 by Himsworth, who observed that elderly or obese diabetic subjects were relatively insensitive to the hypoglycaemic effects of insulin, (9). The advent of radioimmunoassay helped to define IR as "a state in which a greater than a normal amount of insulin is required to elicit a quantitatively normal response", (10). This is compensatory hyperinsulinaemia which occurs when pancreatic β cells increase the output of insulin to maintain normal blood glucose levels due to IR in peripheral, muscle and adipose tissue. Insulin resistance syndrome occurs more commonly in insulin resistant individuals. It is characterized by virilization, acanthosis nigricans, anovulation, acne and defective insulin binding to its receptor on circulating blood lymphocytes. There are two types; A and B (11). When IR is attributable to receptor defect, it is called type A but when it occurs in the presence of circulating anti-insulin antibodies, it is type B. A person with homeostatic model assessment index (HOMA-IR) ≥ 2.5 is considered to be insulin resistant.

Functions of Insulin

The main function of insulin is to balance the body's postprandial energy supply with micronutrient levels (12-13). At the cellular level it influences carbohydrate, lipid and amino acid metabolism and mRNA transcription and translation. Insulin has osteogenic effects and attenuates osteoporosis-related inflammation (14). It acts on the CNS (15) and performs pro- and anti-

atherogenic functions in the vascular system (16). Insulin action in the brain is a physiologic determinant of liver glucose metabolism, (17).

In addition to PCOD, type 2 diabetes, obesity, hypertension, and the metabolic syndrome, insulin resistance (IR) is a frequent medical condition (1,2). Although it has a considerable impact on the development of T2D and the metabolic syndrome, little is known about the underlying mechanisms. It is a complicated metabolic disorder with an intertwined pathophysiology. The treatment of T2D has been hampered by the lack of understanding of IR. To remove TD2 from a fatal diagnosis to a chronic condition that can be addressed therapeutically, a fuller understanding of IR mechanisms is required. Understanding the mechanisms underlying the metabolic syndrome and T2D will reveal novel pharmacological targets. Insulin may have direct and indirect actions on the liver. Directly, it can bind with hepatic insulin receptors to activate PI3K/ PI3K/phosphorylation of the Akt/IRS-1 pathway in the liver which is responsible for the metabolic functions of insulin (18-21). Indirectly insulin can regulate hepatic function via reduction in pancreatic glucagon secretion (22), the inhibition of fat lipolysis (23), and the influence of overall hypothalamic insulin signaling (17, 24), which subsequently affects hepatic glucose production and the later pathway is said to predominate, (12).

In the muscle, insulin stimulates glycolysis and protein synthesis while inhibiting proteolysis. . Skeletal muscle is one of the most dynamic tissues of the human body, and it represents most of the body's weight and its protein. It accounts for almost three quarters of body glucose uptake, (70%. In adipose tissues, insulin stimulates lipogenesis and inhibits lipolysis. Insulin regulates several aspects of adipose cells' functional development and differentiation (25). However, adipose tissue does not depend on glucose but fatty acids released by insulin for use by organs such as the heart (26). Insulin was thought to play no role in brain glucose uptake. Recent evidence suggests some role for insulin in spinal cord and the choroid plexus glucose uptake as well as the control of other vital CNS physiological functions, such as neuronal plasticity, memory processing, and cognition (27-29). Bone cells express insulin receptors that are needed for their proliferation, survival, and differentiation. Insulin being an anabolic agent is capable of increasing the rate of oesteoblastic proliferation, collagen synthesis, alkaline phosphatase activity, and facilitating glucose uptake and subsequent inhibition the activities of oesteoclasts (30, 31).

Mode of Action of Insulin

Understanding IR and its effects requires knowledge of the mechanism of action of insulin. Since insulin cannot enter cells, it attaches to cell surface receptors. The insulin receptor is a hetero-dimer made up of the two subunits and, which are connected by disulfide bonds in the configuration 22 (32, 33). The insulin-binding -subunit (135 kDa) is fully extracellular. The second messenger, or signal transduction, function of the receptor is carried out by the - subunit, a transmembrane protein with a molecular weight of 95 kDa. The cytoplasmic region of the - subunit possesses an autophosphorylation site and intrinsic tyrosine kinase activity. Many things happen when insulin attaches to the receptor. There is conformational change of the receptor.

- The receptors cross-link and form micro aggregates.
- The receptor is internalized.

- One or more signals are generated.

Although the conformational change's relevance is yet unclear, internalization most likely functions as a mechanism for managing receptor concentration and turnover. High plasma insulin concentrations, such as those associated with obesity or acromegaly, lead to a reduction in the number of insulin receptors and a consequent reduction in the sensitivity of target tissue to insulin. This down-regulation is caused by the internalization of receptors, which is the mechanism by which insulin receptors enter cells through the process of endocytosis. Down-regulation explains part of the insulin resistance in obesity and type 2 diabetes (4). The intrinsic tyrosine kinase activity of the receptor is then stimulated by insulin-receptor interaction (34), resulting in the increased phosphorylation of the receptor (35) and specific signaling molecules, insulin receptor substrates, IRS 1-4, on tyrosine residues. Phosphorylation of IRS-2 leads to the activation of phosphotidylinositol-3 kinase, (PI-3K) activity and generation of novel inositol lipids that may act as second messenger molecules. This pathway is involved in the metabolic effects of insulin (36-37) and contributes to the mitogenic action of insulin. The activation of GTPase and stimulation of protein kinase activities, which are crucial in the control of cell proliferation and differentiation, occur as a result of the phosphorylation of IRS-1 in a second pathway. This has no bearing on how insulin affects metabolism; it only adds to its nuclear and mitogenic actions (38-39). It has been demonstrated that insulin activation of the PI-3K pathway is significantly diminished in obese non-diabetic patients and almost nonexistent in type 2 diabetes subjects. In contrast, insulin stimulation of the Erk/MAP kinase pathway was normal in obese and diabetic subjects, (40-41). These signals are linked to the physiological effects of insulin through phosphorylation, dephosphorylation and phosphatase actions brought about by the enzymes activated upstream.

Epidemiology of IR

Generally, the incidence IR is higher in males than females. This is thought to be due to the protective role of oestrogens. Oestrogens are determinants that mediate body adiposity levels and body fat distribution in addition to glucose metabolism and, therefore, insulin sensitivity. Ethnic differences in IR have also been reported (6). IR is a feature of T2D, metabolic syndrome, obesity, acromegaly. It is present in some endocrinopathies such as growth hormone, cortisol, glucagon and catecholamine excess. Differences in the prevalence of T2D have been linked to ethnic/ racial differences in insulin sensitivity, (42). Additionally, a number of modifiable lifestyle factors, including stress, smoking, lack of sleep, diet, and exercise, are known to have an impact on IR. Mikusova *et al* (43), Mengwei *et al.* (8) found a connection between irregular daily eating habits and a greater risk of IR development. Given the prevalence of conditions like metabolic syndrome, type 2 diabetes, and obesity in the general population, IR must also be quite widespread.

Pathogenesis of IR

According to Roach *et al*. (44), LeRoith and Zick (34), IR may be brought on by an inability of insulin to attach to its receptor, a mutation in the insulin receptor itself, a posttranslational alteration of one or both of its downstream effector molecules, or a combination of these factors. It is a phenomenon that is more qualitative than quantitative. According to Granner (4), one cause of IR in obese people is thought to be the receptor downregulation that follows insulin binding. The genetic features of IR may not have received much attention. Various chromosomal regions

were linked to fasting insulin levels, greater triglyceride and lower HDL cholesterol levels, according to some human genetic research.

1. An abnormal beta cell secretion product, (type A) due to:

a) mutation in structural gene for insulin leading to production of biologically defective molecules, (45-46).

b) incomplete conversion of proinsulin to insulin, (47-48).

2. Type B insulin antagonists, which may be or could not be hormonal, are in the blood. Among the identified hormonal antagonists are acknowledged counter-regulatory hormones as cortisol, growth hormone, glucagons, and catecholamines. Adediran et al. (49) claim that they are the cause of the clinical syndrome of insulin resistance in acromegaly. Among the non-hormonal antagonists are anti-insulin and anti-insulin receptor antibodies (48, 50). Exogenous insulin is the cause of antibody production, even if some individuals develop antibodies on their own (47).

3). A target tissue defect in insulin action (type A). This can be a post-receptor or a receptor malfunction. Obesity, T2D, and acromegaly are conditions where there are less receptors (46, 51-52). The spare receptor notion is refuted by the idea that just 10% of insulin receptors need to be bound for the greatest insulin impact. Only when the number of receptors has been lowered to 10% of the intended quantity is a defect by this method achievable, according to Adediran *et al*. (49).

Glucose-Induced IR

By stimulating glycogen synthesis and inhibiting glycogenolysis and gluconeogenesis in the liver, insulin significantly lowers hepatic glucose output and hepatic glucose production (HGP). There are insulin secretory defects which include loss of glucose-induced insulin release. This is seen in diabetes, especially T2D, when high blood glucose levels impair insulin secretion – glucose toxicity. After consuming glucose, type 2 diabetics' insulin concentrations are often lower than those of controls. Instead of glycogen synthase, it has been proposed that glucose transport or its phosphorylation must be the rate-regulating step in insulin-stimulated glucose disposal in skeletal muscle (53). The rate-limiting stage in glycogen production in diabetes and prediabetes, which precedes the onset of T2D, is defective glucose transport into myocytes (54). In such situations, GLUT 4 may be genetically altered. According to Seeley and Woods (55), GLUT-4 gene polymorphism linked to visceral adiposity may encourage insulin resistance. Hyperinsulinaemia, which has been linked to IR and is brought on by long-term consumption of excess glucose, may result from the same process of receptor downregulation as occurs in obesity (56).

Lipid –Induced IR

Earlier definitions of IR had taken a “glucocentric” view since IR is a hallmark of T2D. However recent definitions include “lipocentric” view of the condition since abnormalities in fatty acid metabolism may result in inappropriate accumulation of lipids in muscle, liver, and β-cells and these ectopic lipid accumulations can cause IR in those locations, (so-called “lipotoxicity”), (57-58). When adipose tissue grows excessively as a result of overeating, toxic lipid metabolites (FFA, diacylglycerol, and ceramide) build up in non-adipose tissues, which causes lipid-induced toxicity and the development of IR in the liver and muscle. Insulin stimulates lipid synthesis in liver and fat cells and turn off the release of fatty acids from triglycerides (TG) in fat and muscle tissues,

thus a significant impact on lipid metabolism. Lipid build-up within muscle and liver cells has been observed in diabetics, non-diabetic relatives of T2D patients- a group at high risk of developing the condition, individuals who have impaired glucose tolerance, and over-weight subjects (59-61).

It is believed that fatty acids cause defect in insulin-stimulated glucose transport in skeletal muscle by inhibiting insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and IRS-1 associated phosphatidylinositol 3-kinase activity (54). Their presence promotes fatty acid oxidation that causes the accumulation of mitochondrial acetyl coenzyme A (CoA) and NADH, with subsequent inactivation of pyruvate dehydrogenase. Consequently, intracellular citrate levels rise, leading to inhibition of phosphofructokinase and glucose-6-phosphate accumulation. Glucose-6-phosphate would then inhibit hexokinase activity and cause a decreased intracellular glucose phosphorylation leading to accumulation and decreased glucose uptake (54). A rise in plasma fatty acid concentrations can increase intracellular diacylglycerol (DAG) levels, leading to the activation of protein kinase C isoform (PKC-θ) and PKC-ε isoforms in skeletal muscles and liver respectively. Then there will be a decrease in insulin-stimulated IRS-1/IRS-2 tyrosine phosphorylation, PI3K activation and subsequent insulin signaling that then induces IR in muscles and livers (62). Visceral adipose tissue is of the white type which is metabolically distinct from the brown adipose tissue found elsewhere. It is resistant to antilipolytic action of insulin and so freely releases free fatty acids into the circulation. This increases the flux of free fatty acids directly into the liver and muscles leading to insulin resistance in these tissues (63). Visceral adipose tissues secret inflammatory mediators- leptin, adiponectin, and inflammatory cytokines (tumor necrotic factor- α (TNF-α)) and interleukin-6 (IL-6) that can induce liver and systemic insulin resistance (64). Visceral adipose depot and adipocyte size in humans are also related to insulin resistance (64). Depending on the current glucose content, an acute increase in plasma non-esterified fatty acids (NEFA) is linked to a rise in glucose-stimulated insulin secretion (GSIS). Chronically elevated NEFA is linked to decreased GSIS and insulin production (65). Through its impact on digestive hormones and stomach emptying, fat consumption can alter the insulin response to glucose (66).

Hormone–Induced IR

Like endocrine cells, adipocytes emit a variety of peptide hormones and cytokines, including TNF-, plasminogen-activator inhibitor-1, and leptin, which aids in the mobilization of stored energy. They also produce active steroid hormones, such as cortisol and estrogen (67). Insulin resistance may result from angiotensin-II's interference with insulin's ability to mediate PI3K signaling activation (68). Cortisol, growth hormone, and human placental lactogen are among the hormones that might cause IR (69). They lessen both the activities of insulin to enhance glucose uptake and its actions to regulate glucose synthesis (8).

Obesity-Induced IR

The actions of insulin and glucose metabolism are significantly influenced by a number of adipose tissue secretions, including adiponectin, leptin, chemerin, resistin, visfatin, and vaspin, as well as cytokines and chemokines like tumor necrosis factor-alpha (TNF-), interleukin-6 (IL-6), IL-1, and monocyte chemo attractant protein-1. According to Rabe (70), dysregulation of these adipokines has been linked to the development of metabolic syndromes, IR, T2D, cardiovascular disease, and

obesity. Adeponectin is the most abundant adipokin secreted by adipocytes and it enhances effects of insulin on plasma glucose and fatty acid metabolism and glucose uptake in muscle. It also helps to suppress gluconeogenesis in liver tissues. Adipocytes also produce apelin that enhances glucose uptake and Akt phosphorylation through AMPK pathway to improve glucose homeostasis and insulin sensitivity (71).
According to Ceddia *et al*. (72) and Covey *et al* (73), leptin restricts insulin synthesis and release from pancreatic -cells, increasing insulin sensitivity while decreasing hepatic glucose production and glucagon levels. For several adipokines and bioactive mediators involved in IR pathogenesis, adipose tissue serves as a key node (8).

Consequences of IR
In IR, higher than normal concentrations of insulin are needed for a normal response. There, plasma insulin levels are usually raised glucose tolerance is impaired. IR is linked to metabolic syndrome, a cluster of metabolic disorders may which include obesity, diabetes, nonalcoholic fatty liver disease, cardiovascular disease, polycystic ovary syndrome and other abnormalities, (1-2).

Obesity
Obesity can be a cause or consequence of IR, though either may be true. The arcuate nucleus has a high concentration of insulin and leptin receptors, which regulate energy balance. As a result of the sympathetic nervous system's (SNS) activation and the consequent triglyceride hydrolysis in brown adipose tissue (BAT), diet-induced thermogenesis is a potent phenomenon (74). Insulin is important here (75), and causes increased body temperature and energy expenditure as well as reduced food intake (obesity has hitherto been attributed to increased food intake; (76). Insulin causes increased SNS outflow to BAT to produce heat from fatty acid oxidation. These effects of SNS are mediated primarily by β_3 adrenergic receptor especially in BAT (77). When lipids are metabolized in BAT lipids heat is produced and the body is rid of excess fat. White adipose tissue abounds in subcutaneous and visceral tissues. It serves to store fat which undergoes lipolysis to generate free fatty acids for use by other tissues. β_3 adrenoceptor is important in mediating lipolysis in white adipose tissues in humans. Its activity could promote obesity in several ways: through decreased thermogenesis in brown adipose tissue and through decreased function in white adipose tissues. The later will contribute to visceral obesity in humans. A decreased expression of the β_3 receptor has been detected in genetically obese mice and rats (78), suggesting a role for the receptor in the development of obesity, (79-81). Individuals with this mutation have early on-set type 2 diabetes mellitus, a tendency to low metabolic rate, (95, 79), clinical features of insulin resistance, (80) and increased capacity to gain weight, (81). Action of insulin in the brain is a physiologic determinant of liver glucose metabolism, (17). It has been shown thus far how defective insulin action can lead to obesity. Obesity, however, is a common cause of insulin resistance.

Impaired Glucose Tolerance
Insulin signaling regulates glucose homeostasis by limiting hepatic glucose production via gluconeogenesis and glycogenolysis. These processes consequently increase the glucose uptake rates in muscle and adipose tissues. In addition, insulin profoundly affects lipid metabolism by increasing lipid synthesis in liver and fat cells, in addition to switching-off fatty acid release from triglycerides (TG) in fat and muscle tissues (82). Despite stimulated glucose uptake, insulin rapidly

reduces hepatic glucose output and hepatic glucose production (HGP) by activating glycogen synthesis, and suppressing glycogenolysis and gluconeogenesis in the liver, (61, 83). Adipose tissue's lipid metabolisms, which include enhanced de novo lipogenesis and decreased lipolysis, primarily coordinate with the response of glucose homeostasis to insulin stimulation. Adipose tissue regulates de novo lipogenesis similarly to liver tissue (8). Additionally, it has been demonstrated that the expression of lipogenic genes in adipose tissue substantially and favorably correlates with insulin sensitivity (8). Insulin stimulated protein synthesis is mediated by activation of the protein kinases in numerous insulin-responsive cell types, such as hepatocytes, adipocytes, and myocytes. IR affect different metabolic pathways, such as glucose, lipid, and protein, metabolisms and manifest the typical features of glucose intolerance, T2D and prediabetes. There is overproduction of glucose, the buildup of lipids and protein depletion as seen in diabetes.

Cardiovascular Diseases

Cardiovascular diseases (CVDs) are the leading causes of death globally. The mechanisms by which IR contributes to cardiovascular diseases include chronic hyperglycemia, dyslipidemia, endothelial dysfunction and inflammation. And these result in fasting hyperglycemia in the presence of increased gluconeogenesis and decreased glycogen synthesis. Total TG levels and blood pressure increase, HDL-C levels reduces, and the risk of thrombosis formation increases, (84). Lipotoxicity alters cellular signaling and cardiac structure, thereby contributing to the increased prevalen nce of cardiovascular diseases (85).

Hyperinsulinaemia as seen in IR can cause hypertension by one or a combination of four mechanisms; (1) sodium ion retention; (2) sympathetic nervous system over-activity; (3) disturbed membrane ion transport; (4) proliferation of vascular smooth muscle cells. Elevated plasma insulin concentrations enhance VLDL synthesis leading to hypertriglyceridaemiaInsulin stimulates endogenous lipid production and improves cholesterol transport into arteriolar smooth muscle cells. It enhances the proliferation of and lowers the regression of lipid plaques, stimulates the creation of different growth factors, and boosts the synthesis of collagen in arterial walls. It also stimulates the proliferation of arteriolar smooth muscle cells. According to Jeppesen et al. (86), these are high-risk variables for atherosclerotic cardiovascular disorders.

Liver Diseases

An important function of insulin is nutrient homeostasis and the liver is the primary organ of this action. Though the precise mechanism by which insulin regulates hepatic functions has not yet been elucidated, insulin is thought to acts directly and indirectly on the liver. Directly, insulin can bind with hepatic insulin receptors and activate insulin signaling pathways in the liver (21); indirect insulin action is mostly regulated by the reduction in ancreatic glucagon secretion (22), the inhibition of fat lipolysis (23).and the influence of overall hypothalamic insulin signaling (24), which subsequently affects hepatic glucose production. However, the control of the liver function is largely indirect (90). Iris associated with lipotoxicity which impairs insulin signaling, induces oxidative damage, promotes inflammation and fibrosis (88).

Kidney diseases

Kidney dysfunction is a major cause of morbidity and mortality and its prevalence is rising worldwide (89). A cause-effect relationship has been established between IR

and KD. Several data of different nature consistently support the role of insulin resistance in kidney dysfunction.

Polycystic Ovarian Syndrome (PCOS)

Due to compensatory hyperinsulinemia brought on by PCOS's IR, which activates the GnRH gene's transcription through the MAPK pathway and raises LH pulse secretion, ovarian androgen synthesis is dramatically increased (90). Androgens can directly interfere with insulin signaling, but they can also cause lipolysis and raise blood FFA levels, which can result in IR (91). Furthermore, androgens increase type II muscle fibers (TIIMF), which are glycolytic and less insulin-sensitive, while lowering type I muscle fibers (TIMF), which are highly oxidative and insulin-sensitive, further reducing glycogen synthase expression and encouraging the development of IR in PCOS. (6, 92). This data demonstrates that, in PCOS, IR and hyperandrogenemia continually promote one another in a vicious cycle. By increasing the production of ROS, hyperglycemia may cause oxidative stress and hence inflammation in PCOS patients. In women with PCOS and consequent metabolic problems, obesity and IR are crucial factors.

Assessment of IR

Many methods and indices are available for the estimation of insulin resistance. There are two sets of these indices: those calculated by using fasting plasma concentrations of insulin, glucose and triglycerides and those calculated by using plasma concentrations of insulin and glucose obtained during 120 min of a standard (75 g glucose) OGTT. Detailed discussion of these indices is beyond the scope of this review. However, the gold standard for the assessment of insulin resistance is the hyperinsilinaemic euglycaemic clamp which is a complicated and expensive procedure, (93). A study method known as the frequently sampled intravenous glucose tolerance test can be used for repeated assessments and a large number of patients, according to Lebovitz (94). Due to its simplicity, the homeostasis assessment (HOMA) model (94) is often utilized in clinical practice (49). Only fasting plasma insulin and fasting blood glucose must be measured. The model is generated from a computer program that examines the link between fasting plasma insulin and blood glucose in a sizable group of people who are typically glucose tolerant. A straightforward method for calculating the HOMA index for insulin resistance (HOMA-IR) may be produced from the data.

$$\text{HOMA-IR} = \text{FPI [}\mu\text{U/ml]} \times \text{FPG [mmol/l]}/22.5.$$

Additional methods of evaluation include the quantitative insulin sensitivity check index (QUICKI), the insulin suppression test, the hepatic glucose suppression test, the inhibition of glycolysis, and nuclear magnetic imaging (93). For clinical applications, HOMA-insulin resistance, QUIKI, and Matsuda are appropriate; for epidemiological and research reasons, HES, McAuley, Belfiore, Cederholm, Avignon, and Stumvoll index are applicable.

Insulin has a wide range of metabolic actions and it is critically important to understand whether insulin resistance affects all aspect of insulin actions equally. The half maximum effective concentration of insulin action varies significantly depending on the kind of insulin action tested, as is already known. The response to insulin that inhibits lipolysis seems to be the most sensitive, whereas the response that inhibits glucose oxidation seems to be the least sensitive. Therefore, it

is conceivable that insulin resistance might have a stronger impact on some elements of insulin function than others (2).
It is also important to distinguish the influence of insulin resistance from that of compensatory hyperinsulinaemia that invariably accompanies insulin resistance. If diminished insulin action is the cause of insulin resistance's negative effects, compensatory hyperinsulinaemia is only a bystander with no real impact of its own. Contrarily, the existence of compensatory hyperinsulinaemia may have its own effects if some components of insulin function are not impacted by the decreased potency of insulin. It could amplify or perhaps overamplify some features of how insulin acts in different cells and tissues. It has been shown that decreased activity can coexist with normal, or even increased, insulin action in IR. (Jiang *et al* (95) and Cusi *et al* (40)

Prevention of IR

Risk factors for IR include**:**

- having overweight or obesity, especially truncal obesity
- leading a sedentary lifestyle or lack of exercise
- smoking
- consuming large amounts of alcohol, which can impact the liver
- experiencing sleep issues
- having high cholesterol levels
- having high blood pressure, has been linked to an increased risk of insulin resistance.

These risk factors cannot always be prevented, although some of them could be. Therefore, encouraging lifestyle changes is suggested. There are various actions one may take to lessen the possibility of acquiring insulin resistance. Similar tactics, like controlling weight or giving up smoking and alcohol consumption, have been proven to be successful. Exercise is also beneficial. After exercise, muscles become more insulin-sensitive, assisting the body in reversing insulin resistance. Although receiving an insulin resistance diagnosis might be unsettling, it may still be possible to avoid developing diabetes and other negative effects.

Conclusion

The islet cells of the pancreas create the peptide hormone insulin. It serves as an essential efferent signal to the central nervous system for the regulation of energy balance in addition to serving as a peripheral regulator of nutrient storage and release of circulating substrates. Its functions at the cellular level include mRNA transcription and translation, as well as glucose, lipid, and amino acid metabolism. Insulin promotes bone growth and reduces inflammation brought on by osteoporosis. In IR, hyperinsulinemia and some of its effects are impaired because greater than usual quantities of insulin are required for a normal response. As a result, those with T2D, prediabetes, metabolic syndrome, hyperlipidaemia, PCOS, obesity, cardiovascular, and liver illnesses are more likely to develop these conditions. Understanding IR and its effects requires knowledge of the insulin's mode of action. Due to a lack of knowledge on IR, T2D therapy has been limited. A deeper comprehension of the processes of IR is necessary to turn diabetes from a deadly diagnosis to a

chronic illness that can be treated medically. New pharmaceutical targets for the treatment of T2D and the metabolic syndrome will become apparent as we better understand the molecular/biochemical abnormalities causing IR.

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