RELATIONSHIP BETWEEN INSULIN RESISTANCE AND ASSOCIATED DISEASES: AN OVERVIEW WITH ITS MECHANISM

Shanti Bhushan Mishra[*1]
*United Institute of Pharmacy, UCER, Allahabad (India),

ABSTRACT

Insulin resistance is a common feature in obesity and possibly can lead to further disorders metabolic syndrome like type 2 diabetes mellitus. Lipodystrophies on the other hand are associated with decreased adipose mass but are, again, characterized by insulin resistance. Hyperinsulinaemia, which accompanies IR, is thought to play an important role in the pathogenesis of some syndromes. Excess abdominal adipose tissue has been shown to release increased amounts of free fatty acids which directly affect insulin signalling, diminish glucose uptake in muscle, drive exaggerated triglyceride synthesis and induce gluconeogenesis in the liver. Other factors presumed to play the role in insulin resistance are tumour necrosis factor α, adiponectin, leptin, IL-6 and some other adipokines. In present paper we have discussed about its signaling and mechanism of action of IR.

KEY WORDS: Insulin resistance, Hyperinsulinemia, Insulin signaling, Mechanism of action

INTRODUCTION

Although the current epidemic levels of insulin resistance (IR) and type II diabetes in population have followed the introduction of a " Westernized" lifestyle characterized by high caloric intake and physical inactivity, their prevalence is much higher in these populations than in populations of other ethnic groups with the same lifestyle[1]. In 1988, Gerald Reaven of Stanford University brought together several strands of experimental are epidemiological evidence postulating that resistance to insulin mediated glucose uptake and hyperinsulinaemia affect the development and clinical course of three major related diseases – non-insulin dependent diabetes mellitus (NIDDM), essential hypertension and coronary artery disease [2]. IR is defined as a defect in the ability of insulin to stimulate glucose uptake and results in metabolic syndrome characterized by impaired glucose tolerance and hyperinsulinemia [3]. IR is a central pathophysiological feature of (NIDDM). In addition, IR is a common metabolic abnormality in obesity, hypertension, dyslipidemia, atherosclerosis and recently the term "Syndrome X" was coined to characterized the syndromes of IR-hyperinsulinemia. Environmental non-genetic factors, such as diet, also produce a state of IR but do not cause diabetes [4]. Prospective epidemiological studies across a number of population groups have indicated that IR may be the primary defect in type II diabetes, since it can be detected long before deterioration of glucose tolerance occurs, often at a time when insulin secretion is actually increased. Thus, in many populations and patient groups, IR and hyperinsulinemia precede the development of type II diabetes and can be identified in most prediabetic individuals. Moreover, IR can be further exacerbated during the progression of the disease because of the dysregulation of lipid and carbohydrate metabolism. The β-cells normally respond to peripheral IR by increasing basal and postprandial insulin secretion to compensate for the IR state, maintaining normal or impaired glucose tolerance but preventing frank deterioration of glucose homeostasis and type II diabetes. Eventually, the β-cells are no longer able to compensate for IR by secreting increased amounts of insulin. At this stage, glucose-induced insulin secretion falls, allowing glucose homeostasis to deteriorate and leading to the subsequent development of frank diabetes.

It is clear that the treatment of IR has great therapeutic potential for the amelioration of type II diabetes. Although currently available pharmacological modalities are not directed to the treatment of impaired insulin action, recent

Corresponding author:
Email: shantipharma15@gmail.com
Tel. : +918004279457,
Fax : 91 (0532) 2687142

efforts have focused on the development of insulin-sensitizing agents [5].

Etiological factor to contributing development of insulin resistance

Pathogenesis of IR includes obesity, environment and genetics. "Environment" refers to a variety of factors, including hormones, increased

The nuclear receptor PPAR-γ appears to play a vital role in both adipocyte differentiation and insulin action. PPAR-γ, in particular, has been shown to be involved in regulating genes involved in adipogenesis and by implication, insulin action. Adipogenesis involves a number of transcription factors, including PPAR-γ, C/EBPs and ADD-1/SREBP-1. For instance, the activation of PPAR-γ by TZDs
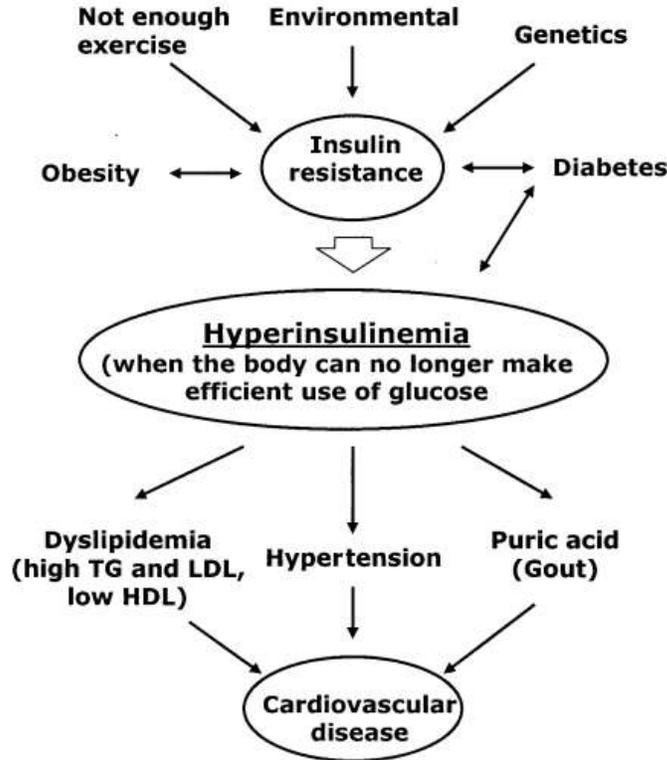

Figure: 1. Insulin resistance and its consequences.

nutrient availability and age.

A) Genetic causes of insulin resistance

Defects in both insulin action and insulin secretion are presented in type II diabetes and both are believed to be genetically predetermined.

Insulin receptor mutation

Receptor autophosphorylation and tyrosyl phosphorylation of other protein substrates require an intact binding site for ATP within the β subunits. Mutation of a critical lysine residue within the site abolishes insulin-stimulated kinase activity and prevents receptor occupancy from generating insulin-stimulated biological actions [6].

Mutations in the peroxisome proliferators-activated receptor γ (PPAR-γ)

enhances adipocyte differentiation and induces gene expression of genes involved in insulin action.

In addition, PPAR-γ activation inhibits leptin gene expression, as well as the expression of TNF-α, which in turn, is an inhibitor of PPAR-γ gene expression. Thus, it is very apparent that PPAR-γ may play a significant role in the pathophysiology of obesity and type-II diabetes [7].

Syndrome associated with extreme insulin resistance

Insulin receptor mutations Leprechaunism, Rabson-Mendenhall syndrome, Type A IR (mutations are relatively uncommon).

Post-binding defects in insulin action Lipodystrophic diabetes syndromes (includes inherited and acquired forms) Type C IR (post-

receptor defect; overlaps with type A). **Insulin receptor antibodies** Type B IR (usually associated with evidence of other autoimmune disease). All of these syndromes are uncommon or rare glucose tolerance may be only minimally impaired if compensatory hyperinsulinaemia is sufficient to overcome the defect[8].

B) Impact of obesity of insulin action

Excess body fat or obesity, is an important factor in the pathogenesis of IR and substantially increases the risk of type II diabetes. Besides being the body's principal site for energy storage, white adipose tissue influences whole body insulin action both through release of FFAs and by secretion of adipose-derived protein. IR in obesity and type II diabetes is manifested by decreased insulin stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output. These functional defects may result in part, from impaired insulin signaling in all three-target tissues and in adipocytes, also from down regulation of the major insulin-responsive glucose transport, GLUTA 4. In muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity and phosphorylation of IRSs are reduced. Another mechanism for the signaling defects in obesity may be the increased expression and activity of several protein tyrosine phosphate (PTPs), which dephosphorylate and thus remainate signaling propagated through tyrosyl phosphorylation events[9].

C) Environmental factors contributing to insulin resistance: Medical conditions that result in insulin resistance:

IR has been reported to result from many medical conditions. IR is also a characteristic feature of renal failure and uremia and improves with dialysis. The cause of the IR in renal failure is likely to multifactorial. Hepatic cirrhosis is frequently associated with glucose intolerance and IR. IR has been recognized in patients with any of several types of cancer, particularly malignancies of the gastrointestinal tract and pancreas. It has been proposed that inflammatory mediators contribute to this IR, particularly TNF-α and IL-6. Potential mechanism whereby these cytokines inhibit insulin action.

Systemic effects of nutrient excess on insulin action

The mechanisms by which changes in nutrient intake alter insulin-signaling events within relevant tissues remain obscure.

Glucose

Glucose toxicity refers to the inhibitory effects of chronic hyperglycemia on insulin secretion and action. Hyperglycemia induced IR includes downregulation of the glucose transport system by hyperglycemia and a defect in insulin-stimulated glycogen synthesis. The subsequent hyperglycemia along with increase in glucose-dependent insulinotropic polypeptide and glucose-link peptide-1 secreted from the gut, stimulate pancreatic insulin secretion, causing an acute rise in plasma insulin concentrations[10]

Pathogenesis of insulin resistance[11]

IR, as determined by the euglycemic-hyperinsulinemic clamp technique, reflects defective insulin action predominantly in skeletal muscle and liver. The major causes of skeletal muscle IR in the prediabetic state may be grouped into genetic background- related and as obesity and physical inactivity-related. Despite intensive research efforts, there is so far no clear understanding of the factors that define the genetic accessibility of IR. One approach for analysis of the genetic background is to define candidate genes based on the present knowledge of the insulin-signaling chain. Abnormalities in insulin signaling that may induce IR in type II diabetes is as follows:

The insulin-signaling chain: Alterations found in insulin resistance and type-II Diabetes

Insulin signaling at the cellular level is mediated by binding of insulin to a specific receptor. Insulin binding to the receptor stimulates autophosphorylation of the intracellular region of the receptor β-subunit. A reduced autoactivation status of the insulin receptor from skeletal muscle and adipocytes of type II diabetic patients has been described by several but not all investigators. Some of these studies have shown that obesity was a major contributory factor for the development of a reduced insulin receptor activity. This could suggest that the defective insulin receptor kinase activity is secondarily acquired due to obesity and metabolic changes such as hyperinsulinemia and hyperglycemia.

Components of Insulin Resistance Syndrome: Insulin Resistance and Inflammation

There is growing evidence that the relationship

between inflammation and IR is not merely correlative but actually causative. Epidemiologic data several large studies have demonstrated a link between IR and systemic inflammation in both type II diabetes and non-diabetic populations. Adipose tissue produces many proinflammatory molecules, including TNF-α, IL-6, transforming growth factor-β, C-reactive protein and monocyte (chemotactic chemoattractant)protein-1 (MCP-1), and circulating levels of these "adipokines" are increased in obesity. Adipose-derived proinflammatory molecules are believed to induce systemic IR and to contribute to the pathogenesis of many metabolic complications of obesity, including type II diabetes and atherosclerosis.

The proinflammatory cytokine TNF-α has been demonstrated to mediate IR as a result of obesity in several rodent models. TNF-α directly decreases insulin sensitivity and increases lipolysis in adipocytes. Expression of TNF-α is increased in white adipose tissue in obese and insulin-resistant states. Multiple mechanisms have been suggested to account for these metabolic effects on TNF-α, including direct effects on insulin signaling, down regulation of genes that are required for normal insulin action, induction of elevated FFA levels via stimulation of lipolysis and negative regulation of PPAR-α[12].

Insulin Resistance and Obesity

Insulin is involved in the regulation of body adiposity via its actions in the central nervous system (CNS) to inhibit food intake and increase energy expenditure. Briefly, insulin receptors are localized in CNS area involved in the control of food intake and energy homeostasis. Insulin administration into the CNS inhibits food intake in animals, including nonhuman primates. Insulin does not enter the brain, but is transported into the CNS via a saturable receptor-mediated process. Using compartmental modeling showed that the obesity induced by a high-fat diet was associated with a 60% reduction of the transport of insulin into the CNS in dogs. This impairment of central insulin transport was inversely related to an increase in body weight in response to high-fat feeding. Specifically, knocking out the insulin receptor in neurons results in hyperphagia and obesity in mice. Thus, reduced insulin delivery into the CNS or disruption of the insulin-signaling pathways in the CNS may result in weight gain and the development of obesity[13].

Insulin Resistance and NIDDM

NIDDM is characterized by progressive impairment of glucose homeostasis and sensitivity to insulin, particularly in skeletal muscle and liver. Oral drug therapy aimed at controlling hyperglycemia in NIDDM often fails, and most patients require insulin treatment late in the course of the disease. This progressive deterioration in glucose metabolism is due, in part, to worsening insulin sensitivity, which may be ameliorated by the glucose-lowering effect of exogenous insulin therapy, but a number of side effects and complications accompany insulin therapy. Therefore, agents, which could augment insulin sensitivity at the level of muscle and liver may be useful in the treatment of IR in NIDDM[14].

Insulin resistance hyperinsulinemia and hyperglycemia

The combination of increased IR and inadequate insulin secretion in response to a glucose challenge will result in hyperglycaemia. Hyperglycaemia increases oxidative stress, defined as the production of the reactive oxygen species (ROS) beyond the protective capability of the antioxidant defences. The two primary mechanisms by which hyperglycaemia may promote the generation of ROS are activation of the polyol pathway, protein glycation and increased glucose auto-oxidation. Hyperglycaemia, hyperinsulinaemia and IR enhance free radical generation and thus contribute to oxidative stress in NIDDM. Oxidative stress associated with hyperglycemia may lead to a reduced number of glucose transporters and impairment of insulin signaling. Oxidative stress can even have adverse effects on β-cell insulin secretion. Therefore, oxidative stress resulting from hyperglycemia and IR can worsen NIDDM by promoting further IR and decreased insulin secretion[15].

Insulin resistance and hypertension

IR is recognized as an important cardiovascular risk factor. The association of diabetes and hypertension potentiates the degree of cardiovascular risk, so recent thereapeutic guidelines recommend to lower blood pressure of hypertensive diabetic patients to levels below those recommended for other hypertensive patients. Indeed, the Hypertension Optimal Treatment Study revealed that lowering diastolic blood pressure in patients with diabetes to 80 mm Hg decreases the risk of major cardiovascular events and

cardiovascular morality compared with lowering the diastolic blood pressure to 90 mm Hg, as recommended for nondiabetic hypertensive patients[16].

Mechanisms that can explain relation between insulin resistance and hypertension are:

1. Insulin can increase blood pressure by increasing renal tubular sodium reabsorption.

2. Insulin increases renal water absorption through proximal tubuli.

3. Insulin could influence blood pressure relates to insulin's ability to enhance sympathetic nervous system activity.

4. Na^+/H^+ counter transport activity is higher in hypertension and IR.

5. When insulin sensitivity decreases Na^+/K^+ ATPase and Ca^{+2}/Mg^{+2} ATPase activities lessen. Increased intracellular sodium by decreased Na^+/K^+ pump activity helps increasing intracellular calcium. Cell becomes more contractile[17].

6. Insulin can decrease the synthesis of vasodilatory prostaglandins, PGI_2 and PGE_2.

Their synthesis needs catecholamine stimulation. Hyper insulinemia may increase peripheral vascular resistance and blood pressure by inhibiting the stimulatory effect of adrenergic agonists on the production of PGI_2 and PGE_2[18].

Insulin Resistance and Dyslipidemia

There are three major components of the dyslipidemia that occurs in insulin resistance.

1. Increased triglyceride levels

2. Decreased HDL and

3. Compositional changes in LDL.

Hyperinsulinemia and the central obesity that typically accompanies IR are thought to lead to overproduction of very low-density lipoprotein (VLDL). The VLDL particle is very complex, containing a number of apoproteins and triglycerides. Some aspects of metabolism are altered in IR that are thought to lead to VLDL overproduction. These are increased FFA and glucose levels that regulate VLDL output from the liver and elevated triglyceride levels in the liver that inhibits apoprotein (apo) B degradation and result in increased assembly and secretion of VLDL. In addition, lipoprotein lipase levels are decreased, which interferes with the normal lipoprotein metabolic cascade and results in decreased clearance of VLDL. The end result is more triglyceride-rich particles, fewer HDL particles and small, dense LDL particles[19]. HDL particles are much smaller than VLDL particles with cholesterol ester in the central core and a variety of apoproteins that govern its metabolism, the atherogenic potential of decreased HDL levels is well known. Possible mechanisms of decreased HDL in IR include 1. Impaired VLDL lipolysis, which depletes HDL by impeding the transfer of apoproteins and phospholipids from triglyceride-rich lipoproteins to the HDL compartment. 2. Exchange between cholesterol ester in HDL and triglyceride in VLDL; 3. Increased activity of hepatic lipase, which facilitates HDL clearance; and 4. Alterations in hepatic function, which inhibit production of apo AI (the main apoprotein of HDL) and/or hepatic secretion of nascent HDL. Elevated LDL is not a characteristic of the dyslipidemia of IR; however, in the insulin-resistant state, the composition of LDL is altered. The LDL particle is characterized by a core of cholesterol ester surrounded by apo B. In small, dense LDL, the cholesterol ester in the core is depleted, apo B increases, and the apo B/lipid ratio is elevated. A preponderance of small, dense LDL is the third principal component of the dyslipidemia of IR. Small, dense LDL appears to be mediated by two mechanisms.

1. An exchange between the cholesterol ester in the LDL and triglycerides in VLDL, which enriches the LDL with triglyceride; lipolysis then depletes the triglyceride, leaving a smaller particle

2. Alterations in VLDL metabolism, in which the VLDL particles are heterogenous, leading to heterogeneity in LDL particles. The altered VLDL metabolism results in production of smaller, denser, cholesterol-depleted LDL particles.

Experimental elevation of the plasma free fatty acid concentration has been shown to lead to IR and inhibition of intramuscular glucose metabolism. Cytokines found in adipose tissue may further contribute to the evolution of IR. The excessive release adipocytokines (eg, tumor necrosis factor-alpha and interleukin-6) and the impaired

release of adiponectin from fat tissue that occur in obesity may contribute to the insulin- resistant state. Accumulation of intracellular triglyceride may also provoke a worsening of β-cell dysfunction, contributing to NIDDM.

Insulin resistance and oxidative stress

Oxidative stress, defined as a persistent imbalance between the production of highly reactive molecular species (chiefly oxygen and nitrogen) and antioxidant defenses, leads to tissue damage. Oxidative stress results from increased content of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). Examples of ROS include charged species such as superoxide and the hydroxyl radical and uncharged species such as hydrogen peroxide[20]. IR and decreased insulin secretion are major features of the pathophysiology of type II diabetes. IR is also caused by acquired factors, such as obesity, sedentary lifestyle, pregnancy and the presence of excess hormones.

In-vitro and *in-vivo* studies suggest that in a variety of tissues, hyperglycemia and possibly elevated FFA levels (both alone and in combination) result in the generation of ROS and RNS and consequently increased oxidative stress. The reactive species not only directly damage cells by oxidizing DNA, protein and lipids but indirectly damage cells by activating a variety of stress-sensitive intracellular signaling pathways such as NF-$_k$B, p38 MAPK, JNK/SAPK, hexosamine, PKC, AGE/RAGE, sorbitol, and others. Activation of these pathways results in the increased expression of numerousgene products that also cause cellular damage and play a major role in the etiology of the late complications of diabetes. The ROS and oxidative stress induced by elevations in glucose and possibly FFA levels play a key role in causing insulin resistance and β-cell dysfunction by their ability to activate stress-sensitive signaling pathways[21].

Insulin resistance and endothelial dysfunction

The term endothelial dysfunction has been used to refer to several pathological conditions including altered anticoagulant and anti-inflammatory properties of the endothelium, impaired modulation of vascular growth and dysregulation of vascular remodeling. Impaired endothelium-dependent vasodilation in the coronary circulation of humans has profound prognostic implications in that it predicts adverse cardiovascular events and long-term outcome. A decline in NO bioavailability may be caused by decreased expression of the endothelial cell NO synthase (eNOS), a lack of substrate or cofactors for eNOS, alterations of cellular signaling such that eNOS is not appropriately activated and finally accelerated NO degradation by ROS. This tenuous balance seems to be altered in a variety of common disease states. One of the first examples of this came from studies of hypercholesterolemic rabbits. These animals have severely impaired endothelium-dependent vascular relaxation, suggesting a lack of NO$^\bullet$. Paradoxically, the production of total nitrogen oxides (NO$^\bullet$ and oxidation products of NO$^\bullet$) was increased by as much as 3-fold in these vessels. Furthermore, nitrogen oxide production increased appropriately on stimulation with either acetylcholine or the calcium ionophore A23187, suggesting that signaling pathways leading to eNOS activation were intact in these vessels. These findings led to the speculation that hypercholesterolemia could result in oxidation of NO$^\bullet$ to vaso- inactive nitrogen oxides (such as nitrite and nitrate). Subsequently, it was shown that treatment of cholesterol-fed rabbits with polyethylene-glycolated-SOD could markedly enhance endothelium dependent vascular relaxation but have no effect in normo cholesterolemic animals. This observation strongly supported the concept that in hypercholesterolemia, nitric oxide bioavailability is reduced by O[22].

Subsequently, altered endothelium-dependent vascular relaxation has been associated with enhanced degradation of NO$^\bullet$ by ROS in animal models of many different diseases. These include hypertension, diabetes, cigarette smoking and heart failure. These studies have been extended to humans. Antioxidant vitamins have been shown to enhance endothelium-dependent vasodilation in both the coronary and forearm circulations in subjects with any of the same diseases examined in animal models[23].

Insulin resistance and vascular tissue

IR and possibly hyperinsulinemia have been suggested as risk factors for the development of cardiovascular complications in diabetes. In hyperglycemia the increased amounts of glucose can be transported intracellularly and metabolized to increase flux through sorbitol pathway, change the

redox potential or alter signal transduction pathways, such as the activation of the diacylglycerol (DAG) and protein kinase C (PKC) levels. The activation of DAG-kinase pathway causes increased expression of transforming growth factor-b (TGF-b), which has been implicated in the development of mesangial expansion and basement membrane thickening in diabetes. The increased PKC and cytosolic phospholipase A$_2$ (cPLA$_2$) activities result in increase of arachidonic acid release, prostaglandin E$_2$ (PGE$_2$) production and decrease in Na$^+$-K$^+$ ATPase activity. PKC activation can also regulate vascular endothelial growth factor (VEGF). Similarly, the PKC activation also causes the expressions of plasminogen activator inhibitor-1 (PAI-1) and endothelin-1 (Et-1) leading to increased contractility and coagulation respectively. Thus, activation of the PKC pathway can, in vascular cells, regulate permeability, contractility, extracellular matrix, cell growth, angiogenesis, cytokine actions, and leukocyte adhesions, all of which are abnormal in diabetes [24, 25].

Molecular mechanisms of insulin resistance[26]

The IR at molecular levels appears to occur at the level of G-protein, Kinase activation, glucose carriers (GLUT) and gene expression.

G-proteins and their role in insulin resistance

Insulin binds to insulin receptor dimmers activating tyrosine kinase and large trimeric α, β, γ G proteins. Tyrosine phosphorylated IR β-subunits bind several docking proteins via SH2 domains, IRS is shown as one example. Large G proteins, in turn activate small G proteins by as yet unknown mechanisms which in turn activate membrane phospholipases C and/or D to cleave glycosyl phosphatidylinositol lipid (GPI)s to water soluble inositol phosphoglycan (IPG)s on the outer membrane surface. IPGs enter cell of origin or neighboring cells by an autocrine paracrine mechanism and active IRS tyrosine such as Src recruited to the membrane by the dissociated β, γ subunits of the large G proteins. Tyrosine phosphorylation of IRS mediated by IPGs then constitute a mechanism of cross-talk with the direct insulin receptor-initiated tyrosine kinase cascade. The inhibition of insulin signaling by pretreatment with rat adipoctes, hepatocytes and BC3 H1 myocytes with pertussis has been well documented indicating the involvement of Gi or Go proteins in defective insulin signaling. All these reports suggest the possibility of abnormal functioning of G-proteins in the insulin resistant state.

Kinases and their role in insulin resistance:

Insulin receptor is a ligand-activated tyrosine protein kinase. Binding of insulin to the alpha subunits of the heterotertrameric insulin receptor leads to the rapid intramolecular autophosphorylation of several tyrosine residues in the beta subunits. In the intact cells, the insulin receptor is also phosphorylated on the serine and threonine residues presumably by protein kinase C or cyclic AMP dependent protein kinase, such phosphorylation inhibits tyrosine kinase activity of the insulin receptor. The tyrosine kinase activity is required for the signal transduction. The activated receptor kinase initiates a cascade of events first by phosphorylating a protein called insulin receptor substrate-1 (IRS-1). Phosphorylated IRS-1 serves as a docking protein for the other proteins that contain so called Src homology 2 (SH2) domains. One of such SH2 domain proteins is phosphoinositide PI-3-kinase. PI-3 kinase catalyzes the addition of phosphates to phosphoinositides on the 3-position of the D-myoinositol ring and this compound is one of the most potent mitogens. RAS has been linked to insulin action pathway because it is known to activate the cascade of the mitogen activate protein (MAP) kinases. MAP kinases are among the many of such kinases that are known to be activated by insulin. Insulin also activates serine/threonine phosphorylation cascades. Serine kinases have a dual function in the insulin signaling pathway i.e. further transduction of the insulin signal and activation of glycogen synthase or MAP kinase activation. IR seems to involve specifically the MAP kinase and PI-3 kinase activation.

Glucose transporters and their role in insulin resistance

Glucose transport in skeletal muscle and adipose uptake tissue is insulin sensitive and is normally considered to be rate limiting for glucose uptake and utilization. Therefore, reduction in the number of glucose carriers could be another possible reason for the interruption of the signal flow. In NIDDM, the protein content of adipose tissue GLUT4 (a major glucose transporter) is reduced and its translocation from intracellular stores in response to insulin stimulation is impaired. In skeletal muscle GLUT4

expression is normal, but its translocation is impaired and insulin signaling is probably defective. Recently it has been reported that a mutation in the GLUT2 glucose transporter gene of a diabetic patient abolishes transport activity. The presence of this mutation in a diabetic patient abolishes transport activity. The presence of this mutation in a diabetic patient suggests that defective in GLUT2 expression may by causally involve in the pathogenesis of IR.

Role of gene expression in insulin resistance

Alterations in the various enzymes and proteins mentioned above are mediated through a change in rate of mRNA synthesis from specific genes. Various mutations have been detected in the insulin receptor gene in patients with genetic syndromes of extreme IR. A mutation in the structural gene coding for the transacting factor that impairs its ability to bind DNA or that effects the rate of transacting factors may be involved e.g. unrestricted gluconeogenesis is the primary source of the excessive overproduction of glucose in NIDDM. Because phosphoenol pyruvate carboxykinase (PEPCK) catalyzes the rate-limiting step in gluconeogenesis. It is possible that faulty regulation of the PEPCK gene could be involved in IR.

"Diagnosing" the Insulin Resistance Syndrome[27]

The precise way in which IR develops is unclear, although genetics, diet and level of physical activity are believed to play a role. Identifying patients with IR and those who are likely to develop IR offers the hope that some or all of the components of syndrome can be prevented. The most accurate way to measure IR is the euglycemic insulin clamp technique, in which insulin level glucose is then infused an, as the plasma level falls because of the action of insulin-more glucose is added to maintain a steady level. The amount of glucose infused overtime provides a measure of IR. There is a strong relationship between abdominal obesity and the degree of IR independent of total body weight.

Identifying abnormalities of insulin resistance syndrome:

1. Triglycerides >150 mg/dL

2. HDL cholesterol< 40-50 mg/dL

3. Blood pressure >130/85 mmHg

4. Glucose: Fasting – 110-125 mg/dL ,120 min post-

glucose challenge 140-200 mg/dL

Factors that increase the likelihood of the insulin resistance syndrome

1) Diagnosis of CVD, hypertension, and Acanthosis nigricans.

2) Family history of type 2 diabetes, hypertension or CVD.

3) History of gestational diabetes or glucose intolerance

4) Sedentary lifestyle

5) BMI > $250/mg/m^2$

6) Age > 40 years

Measuring Insulin Sensitivity[28]

The gold standard for assessing IR and insulin sensitivity is the hyperinsulinemic- euglycemic clamp technique; however, this test is too labor intensive, time consuming and costly for routine clinical practice. The homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICK) can be used alternatively as minimally invasive, surrogate measures of insulin resistance that are easy to apply in a standard office setting and provide reasonable indices of insulin action in prediabetes and diseases of recent onset. Both measures are calculated using simple mathematical transformation of standard clinical biochemistries.

HOMA = (Fasting insulin x Fasting glucose)/ n

n = 405 (if fasting glucose values in mg/dL)

n = 22.5 (if fasting glucose values in mmol/L) QUICK1=1/[log (fasting insulin) + log(fasting glucose)]

DISCUSSION & CONCLUSION

IR and hyperinsulinaemia, some special impairments, e.g. vascular or ovarian defects, could finally contribute to the full development of IR related diseases. A combination of genetic and environmental factors should therefore be considered and the aetiological mechanisms of these diseases need to be studied further. This is particularly important in the case of metabolic syndrome, as there is still some doubt about whether it exists or whether it is merely the random co-existence of cardiovascular risk factors without any common origin. Future study of the molecular mechanisms of IR-associated diseases would help in

the management of their frequent and serious complications, DM2 and coronary heart disease.

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LIST OF ABBREVIATIONS USED

ATP -   Adenosine triphosphatase, ET-1 - Peptide endothelin-1, FFAS - Free fatty acids

HDL -   High-density lipoproteins, HOMA - Homeostasis model assessment

IGF -   Insulin like growth factor, IL-6 - Interleukin - 6, IR - Insulin resistance

LDL -   Low-density lipoproteins, NIDDM - Non-insulin dependent diabetes mellitus

PPAR-γ- Peroxisome proliferators-activated receptor- γ,

QUICK- Quantitative insulin sensitivity cheek index, RNS - Reactive nitrogen species

ROS -   Reactive oxygen species, TNF-α - Tumor necrosis factor-α

VEGF -   Vascular endothelial growth factor, VLDL - Very low-density lipoproteins

IRS -   Insulin receptor substrate