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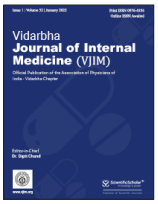

Review Article

Insulin Resistance

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ABSTRACT

The twin epidemic of 'Diabesity'-diabetes and obesity, all over the world, both in developed and developing countries, has brought the issue of insulin resistance (IR) into new focus of research. Apart from Type 2 diabetes mellitus (DM), IR is implicated in many other clinical syndromes because of its varied metabolic and mitogenic actions. IR has been found to play important pivotal role in pathophysiology of diabesity. IR is defined as when a normal or higher insulin level fails to produce expected biological response; one predominantly affecting insulin mediated glucose disposal. 20–30% reduction in the number of insulin receptors on the target cells is observed in majority of Type 2 DM patients but 1/3 of the patients may not manifest loss of number of receptors; therefore, defective post-receptor signalling is considered as the main cause of IR. Main sites of IR are liver, adipose tissue and skeletal muscles. Apart from Type 2 DM, many other clinical and genetic syndromes are associated with IR.

Keywords: Insulin resistance, Hyperinsulinaemia, Insulin receptor, Metabolic syndrome

INTRODUCTION

The twin epidemic of 'Diabesity'-diabetes and obesity, all over the world, both in developed and developing countries, has brought the issue of insulin resistance (IR) into new focus of research.

Apart from Type 2 diabetes mellitus (DM), IR is implicated in many other clinical syndromes because of its varied metabolic and mitogenic actions. IR has been found to play important pivotal role in pathophysiology of diabesity.

SOME KEY CONCEPTS

IR is defined as when a normal or higher insulin level fails to produce expected biological response;[1] predominantly affecting insulin mediated glucose disposal.[2]

Compensatory hyperinsulinaemia occurs because of excess insulin secretion by islet beta cells to compensate for the peripheral resistance to insulin action.

Metabolic syndrome is the collection of abnormalities that occur in insulin resistant subjects. Some of these abnormalities are due to insulin excess while some are due to resistance to insulin actions.[2]

HISTORY

Nobel prize was awarded to Best and Macleod in 1923 for discovery of insulin. The theory of IR as cause of Type 2 DM was first postulated by Prof William Falta in 1931 at Vienna which was confirmed by Sir Harold Himsworth in 1936. He observed wide differences in hypoglycaemic effects of similar doses of insulin in different sets of patients with diabetes and suggested that some patients are hyperglycaemic because of resistance to action of insulin rather than from lack of insulin. This was confirmed later in 1960 by Yalow and Berson who reported a set of Type 2 DM patients who were hyperinsulinaemic rather than insulin deficient.[3]

INSULIN SECRETION

Amount of insulin secreted by beta cells, required for facilitating entry of glucose into the cells and for control of lipolysis and gluconeogenesis, thereby maintaining normal fasting blood glucose is 0.25–1.5 units/hour in basal or fasting state.

Over 50% of total daily insulin is secreted as basal insulin while remaining 50% of secretion is meal related. About 60% of total insulin secreted into portal vein is removed by the liver. In fed state, insulin promotes glycogen and lipid synthesis in muscle cells and suppresses lipolysis and gluconeogenesis from muscle amino acids.

INSULIN RECEPTORS

Insulin action is exerted by binding to insulin receptors. Insulin receptor is a heterotetramer of 2α and 2β glycoprotein

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subunits linked by disulphide bonds located on the cell membrane.[4] Insulin molecule binds to the extracellular α subunit, which results in binding of ATP to the intracellular β subunit [Figure 1]. This causes activation of tyrosine kinase enzyme and triggers phosphorylation of the β subunit. This reaction further leads to tyrosine phosphorylation of intracellular substrate proteins known as insulin responsive substrates (IRS). Binding of IRS with other signalling molecules mediates further cellular actions of insulin[4] such as activation of Phosphoinositol 3 kinase (PI3-K) finally resulting in translocation of Glucose Transporter 4 (GLUT4) to the cell membrane, thus facilitating transport of glucose into the cell. This also brings about other effects of insulin on various metabolic functions such as protein synthesis, glycogen synthesis and antilipolytic effect.

CELLULAR MECHANISMS OF IR

About 20–30% of reduction in the number of insulin receptors on the target cells is observed in majority of Type 2 DM patients but 1/3 of the patients may not manifest loss of number of receptors; therefore, defective post receptor signalling is considered as the main cause of IR.

Even compensatory hyperinsulinaemia with maximal binding with receptors fails to achieve normal disposal of glucose; hence, the focus is on steps beyond post-receptor binding. Approximately 80% of decrease in insulin stimulated phosphorylation of IRS and 90% decline in PI3-K release have been observed in animals with IR, resulting in non-migration of GLUT4 units to cell membrane. A 50% of decrease in glycogen synthesis is the major defect in glucose disposal at myocyte level.

MAJOR POST-RECEPTOR SITES INVOLVED IN IR

- Tyrosine kinase generation
- P13-K post-binding signal transduction
- Glut 4 translocation
- Glycogen synthesis.

SITES OF IR

Skeletal muscles

Skeletal muscle is the major site for disposal of about 75% of excess plasma glucose after a meal or glucose load by glucose uptake and conversion into glycogen, as assessed by euglycaemic clamp technique. Adipose tissue mass being smaller in size, accounts for the rest. Various research methods have shown that defective insulin stimulated glycogen synthesis in skeletal muscles is the hallmark of IR in Type 2 diabetics.[5] IR in skeletal muscle cells correlates well with triglyceride content of the muscle, insulin stimulated glucose uptake is inversely related to the intramyocellular triglycerides.

Liver

A major action of insulin is to suppress endogenous hepatic glucose production (HGP). While postprandial hyperglycaemia in diabetes is due to diminished uptake of glucose by muscles, in fasting state, uninhibited HGP secondary to excess glycogenolysis and gluconeogenesis as a result of IR at hepatic level is the main reason. Therefore, raised fasting sugar despite elevated fasting insulin is strong indication of IR. Lipoprotein metabolism in liver is also affected by IR. Triglyceride and very low-density lipoprotein (VLDL) levels rise because of increased free fatty acids (FFAs) delivery to liver and reduced catabolism of VLDL in insulin resistant adipocytes. Small dense low-density lipoprotein (LDL) particles are also increased in the process.

Adipose tissue

IR is closely related to obesity. Increased body mass index (BMI), waist circumference and in particular waist-hip ratio increase the IR.[6] Increased intra-abdominal fat around the intestines correlates closely with liver fat. This visceral fat is more metabolically active with regard to FFA turnover as compared to subcutaneous fat. Lipogenesis and lipolysis in adipose tissue are most sensitive to regulation by insulin. IR results in accelerated lipolysis with flooding of circulation with FFA. Adverse metabolic effects of plasma FFA are termed as lipotoxicity. Excess FFA is instrumental in accumulation of triglycerides in skeletal muscle cells and hepatocytes, which reduces insulin sensitivity for glucose uptake. Excess lipids within beta cells impair their secretory function. Furthermore, since lipoprotein lipase activity is insulin-dependent and impaired by IR, peripheral uptake of triglycerides from VLDL is also diminished. These mechanisms contribute to the hypertriglyceridaemia of IR.[7]

While excess fat in obesity leads to IR, complete lack of it as in lipodystrophy is also associated with serious significant IR, probably due to accumulation of fatty acids in tissues other than adipocytes and/or due to lack of some adipokines.

Adipose tissue also acts as endocrine organ and produces adipokines such as leptin and adiponectin and many inflammatory mediators such as tumour necrosis factor alfa, Interleukin 6 and Plasminogen Activator Inhibitor 1 (PAI 1). Obesity is a chronic mild inflammatory state because of inflammatory cytokines produced in excess. These inflammatory cytokines and leptin are associated with increased IR, while adiponectin reduces IR.[8] In patients with diabetes or those having IR, the adipocytes show defective intracellular signalling, defective GLUT4 translocation and impaired insulin stimulated PIP3 kinase activity.[9]

Obesity, hyperphagia, infertility and IR are seen in Ob mice or leptin deficient mice. Exogenous leptin administration is shown to reverse these abnormalities and decrease IR in

these mice. In human beings, congenital leptin deficiency is associated with grossly increased appetite, morbid obesity and IR.

Brain

Leptin and insulin appear to share a common signalling pathway in the hypothalamus.[8] There is suggestion of a potential link to Alzheimer's disease, given insulin's role in normal cognitive functioning and the regulation of amyloid precursor protein.

DRUGS AND IR

Many commonly used drugs are found to affect insulin sensitivity. Metformin reduces IR in liver and reduces hepatic glucose output. It also reduces IR at peripheral level, but to a lesser extent. Thiazolindeons for example, rosy and pioglitazone, are more potent in reducing peripheral IR. They also promote redistribution of hepatic and visceral adipose fat to the subcutaneous tissues, thereby reducing harmful central obesity. They improve IR in adipose tissue but not in muscle and are shown to be effective in polycystic ovarian syndrome (PCOS).[10] Use of glitazones is limited by their side effects.

Corticosteroids and oral contraceptives increase IR due to their counter regulatory action. Protease inhibitors used in treatment of HIV result in partial lipodystrophy with increase in abdominal fat and increase in IR with loss of subcutaneous fat.

CLINICAL SYNDROMES ASSOCIATED WITH IR

T2DM

IR precedes clinical manifestations of T2DM. It is also seen more commonly in first degree relatives of T2DM patients.[10] Insulin-mediated GLUT4 translocation is defective, and peripheral glucose uptake by muscle cells and adipocytes is affected resulting in hyperglycaemia.[10] First phase of insulin secretion is lost early in the course of the disease despite compensatory hyperinsulinaemia. Additional environmental and physiological stresses such as pregnancy, weight gain, physical inactivity and medications may worsen the IR.

Metabolic syndrome

The Adult Treatment Panel III of the National Cholesterol Advisory Panel defines metabolic syndrome as the 'constellation of lipid and non-lipid risk factors of metabolic origin'. It was initially called as syndrome X but was later named as metabolic syndrome. It was observed that individuals having the features of this syndrome were prone to increased cardiovascular risk.[2] At least three of the following features are required for diagnosis of metabolic syndrome:

- Abdominal obesity with waist circumference in males more than 40 inches or 102 cm and in females more than 35 inches or 88 cm
- Fasting blood sugar between 110 and 126 mg/dL (6.1–7.0 mmol/L)
- Blood pressure more than or equal to 130/80 mmHg
- Triglycerides more than 150 mg/dL (1.7 mmol/L) with high-density lipoprotein (HDL) cholesterol in men <40 mg/dL (1.0 mmol/L) and in women <50 mg/dL (1.3 mmol/L).

Dyslipidaemia

IR affects all lipid fractions resulting in raised fasting triglyceride levels, elevated postprandial triglyceride-rich remnant lipoproteins, low HDL cholesterol and increased small dense LDL particles. These lipid abnormalities greatly increase the individual's cardiovascular risk, which can be reduced with treatment.[2]

Hypertension

Compensatory hyperinsulinaemia secondary to IR leads to increased renal sodium retention and increased sympathetic activity, resulting in hypertension.[2] This is observed in almost 50% of patients with IR.[11] Endothelial dysfunction from resistance to insulin-mediated nitric oxide formation is also implicated in causing hypertension.

Pregnancy

High levels of various hormones in third trimester of pregnancy, such as human placental lactogen, progesterone, oestradiol and cortisol, in combination act as counter-regulatory hormones to insulin. This exaggeration of the IR in pregnancy is responsible for gestational diabetes mellitus and gestational hypertension.

PCOS

IR is linked to PCOS, common endocrine disorder of premenopausal women associated with infertility, obesity, acanthosis nigricans and skin tags. Hyperinsulinaemia increases pituitary Leutinizing Hormone (LH) secretion and androgen production by the ovary. Function of the hypothalamo-pituitary gonadal axis is further affected by aromatisation of androgens with increased production of oestrogens, in presence of obesity. High insulin levels also suppress hepatic Sex Hormone Binding Globulin (SHBG) production, further increasing free androgens levels which in turn further aggravate IR. Treatment modalities such as weight loss, exercise and drugs such as metformin and glitazones help in reducing IR and improving ovarian function.[10]

Non-alcoholic fatty liver disease

Peripheral IR in fat and muscle leads to increased delivery of FFAs to the liver, increasing triglyceride synthesis. Fatty liver develops when hepatic triglyceride synthesis exceeds hepatic synthesis and export of VLDL triglyceride.[2]

Cancer

Hyperinsulinaemia with IR has been implicated in the aetiology of certain cancers, including colon, endometrial, and possibly pancreatic and renal-cell cancers and breast cancer.[2] Elevated insulin-like growth factor 1 levels promote intestinal epithelial cell proliferation. In addition to mitogenic effects of insulin itself, the effects of IR on ovarian function and sex hormone metabolism, along with low levels of SHBG potentially elevating bio-available hormone levels, may also contribute to carcinogenesis.

Obstructive sleep apnea (OSA)

Although OSA is considered as complication of obesity, OSA may be a systemic condition related to IR.[2] However, the resultant sleep deprivation may increase IR via activation of the HPA axis. Treatment of OSA by nasal Continous positive Airway pressure (CPAP) preferentially decreases visceral adipose tissue. Instead of IR contributing to OSA, OSA might contribute to IR.

UNCOMMON GENETIC DISORDERS ASSOCIATED WITH IR

Many genetic disorders such as Turner's syndrome, Klinefelter syndrome, Down's syndrome, progeria, Laurence Moon Bible syndrome, Huntington's chorea, haemochromatosis, lipodystrophy, and glycogen storage disease are associated with IR.[12]

MEASUREMENT OF IR

IR can be measured by many research methods as well as by clinical and laboratory parameters. It may be assessed by measuring insulin mediated glucose uptake in the basal or postprandial state or by inference from the relative concentrations of glucose and insulin or by measuring surrogate markers of insulin action.[13]

RESEARCH METHODS

The clamp studies specifically measure insulin mediated glucose uptake under controlled conditions. These include the euglycaemic clamp (considered the gold standard) and the hyperinsulinaemic clamp. Insulin sensitivity tests and short insulin tolerance tests are comparatively less invasive. Assessments of IR based on mathematical modelling include the Homeostasis Assessment Model[14] and the Quantitative Insulin Sensitivity Check Index, Continuous Infusion of Glucose with Model Assessment, Frequently Sampled Intravenous Glucose Tolerance Test and minimal modelling are indirect methods of IR measurement.

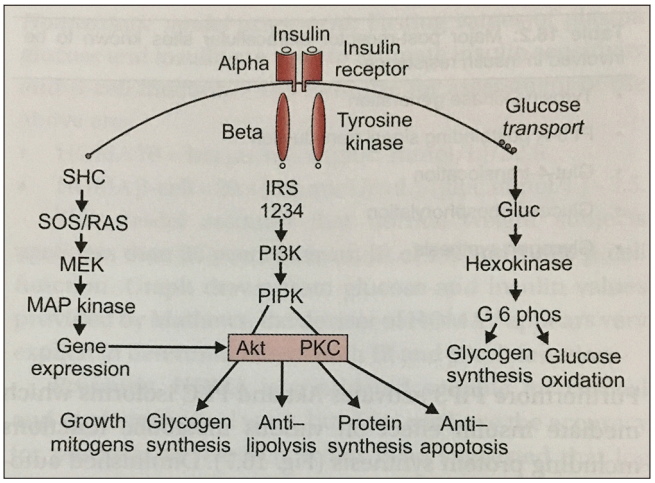

Figure 1: Insulin receptor and intracellular signalling (Courtsy-RSSDI Textbook of Diabetes Mellitus, 3rd Edition).

CLINICAL METHODS

Fasting plasma insulin assay is much simpler method for measuring IR as compared to complex research methods.

FUNCTIONAL MEASURES

IR can also be diagnosed by functional markers such as BMI, serum triglyceride concentration, ratio of triglyceride to HDL cholesterol concentrations and insulin concentration. Cut points of 1.47 mmol/L for triglyceride, 1.8 mmol/L for the triglyceride-HDL cholesterol ratio and 109 pmol/L (16 mIU/L) for insulin are quite specific and sensitive indices for diagnosis of IR.[15]

CONCLUSION

Apart from genetic or biological causes, social and environmental factors are equally important in causation of IR. Rapid globalisation, urbanisation and industrialisation are responsible for epidemics of obesity, diabetes and related comorbidities.[13] Dramatic social changes of the past century with respect to physical activity, diet, work, socialisation and sleep patterns need to be addressed seriously if we want to deal with problem of IR.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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