International Physiology
Vol. 3 No. 2, July - December 2015
DOI: https://dx.doi.org/10.21088/ip.2347.1506.3215.7

Insulin Resistance in Type 2 Diabetes Mellitus & Scope of Triglyceride / High Density Lipoprotein-C Ratio as a Marker of Insulin Resistance in Patients with Metabolic Syndrome

Zingade

Insulin resistance is a hallmark of Metabolic Syndrome. It is important to identify insulin resistance at an early stage of Diabetes mellitus. There are many indicators used traditionally for measurement of insulin resistance like HOMA-IR (Homeostasis Model Assessment of Insulin Resistance); QUICKI (Quantitative Insulin Sensitivity Check Index) and ratio of Triglyceride / High density Lipoprotein–C. There is a positive correlation between HOMR-IR and TG/HDL-C ratio and negative correlation between QUICKI and TG/HDL-C ratio. In following discussion; the pathophysiology of metabolic syndrome and it's relation with Insulin Resistance is discussed.

Pathophysiology of Insulin Resistance in Metabolic Syndrome

Patients with type 2 DM share a pathophysiology that involves pancreatic β cells, liver and peripheral target tissues namely skeletal muscles, adipose tissue. Both β cell dysfunction and insulin insensitivity result in hyperglycemia. Glucose uptake in skeletal muscles requires insulin binding to cell receptors; which facilitates movement of glucose across cell membrane. The glucose is then utilized as a source of energy via glycolysis to produce lactate or mitochondrial oxidation or is stored as glycogen in the cell. Hormones and/or cytokines produced by adipose tissue also plays an important role in glucose and fat metabolism and are likely to contribute in pathophysiology of DM. Free Fatty acids play an essential role in Type 2 DM by inducing insulin resistance and facilitating excessive glucose production by liver.

Normal Physiology of Glucose Homeostasis

Maintenance of glucose levels depends on feedback between blood cells and pancreatic hormones i.e., glucose and insulin levels. Glucose is produced by liver by glycogenolysis and neoglucogenesis. Approximately 70-80% of the glucose produced by liver is utilized by brain (Insulin independent tissue) and other insulin sensitive tissues i.e. intestinal mucosa and RBCs, Retina, Skeletal muscles and Fat require insulin for utilization of glucose. Thus at the hepatic level, Hepatic glucose output (HGO) is regulated by:

(i) Insulin, glucagon, catecholamine, glucose level itself on short term basis (minutes-hours).

(ii) GH, T3, T4, Glucocorticoids on long term basis (hours to days).

Insulin exerts an inhibitory effect on HGO. Thus decrease in insulin levels causes slow rise in HGO. If the feedback loop is intact, as serum glucose level rises, insulin secretion also rises and glucagon level decreases. If insulin resistance develops, a new steady-state higher glucose level is reached.

At the Cellular level

Insulin binds with cell receptor which activates receptor's tyrosine kinase activity. This activation triggers a molecular phosphorylation signaling a cascade reaction. Insulin receptor substrate 1 & 2 activation causes activation of:

(i) PI 3 kinase (phosphatidyl inositol 3 kinase),

(ii) CAP / cbl / Tc10 pathway (CAP- cCbl associated protein),

Author's Affiliations: Professor & H.O.D. (BJMC, Pune) Maharashtra State.

Corresponding Author: U. S. Zingade, 10a, Mohite Twonship, Sinhgad Road, Near Santosh Hall Hingne, Khurd, Pune-411051.

E-mail: uszingade@gmail.com

(iii) ERK pathway (extracellular signal regulated kinase).

Ultimate result of the activation is translocation of the GLUT 4 protein from cytoplasm to cell membrane which facilitates influx of glucose into the cell for subsequent metabolism.

Natural History and Epidemiology of Insulin Resistance

Insulin resistance is present in approximately 90% of patients with type 2 diabetes. IR is often associated with metabolic abnormalities (known as metabolic syndrome, dysmetabolic syndrome, insulin resistance syndrome, Syndrome X, Reaven's syndrome). This syndrome is identified by hypertension, hyperglycemia, glucose intolerance, dyslipidemia, abdominal (central) obesity, endothelial dysfunction, impaired vascular reactivity, vascular inflammation and impaired fibrinolysis. Some or all of these components may be present in any given patient.

Even though associated with Metabolic Syndrome insulin resistance also occurs in a person who is not diabetic (up to 25% of non-diabetic patients. have lower degree of insulin sensitivity).

Although more common in older people, there is an increasing number of children and teenagers having insulin resistance. Generally Insulin resistance progresses and worsens over a period of years. With worsening of insulin resistance, insulin is less able to dispose of glucose from blood. In order to maintain euglycemia, there is compensatory hyperinsulinemia. However β cells gradually decrease functionally resulting in prediabetes and then type 2 Diabetes.

For clinicians, it is challenge to identify persons who are at risk as early as possible where interventions are likely to be more effective.

Insulin Resistance

Insulin resistance is defined as a condition of low insulin sensitivity in which the ability of insulin to lower circulating glucose is impaired. Along with genetic determinants other factors like obesity, aging, elevated FFA and hyperglycemia contribute to insulin resistant state. Biochemical defects that provoke insulin resistance involve impaired insulin signaling and reduction of glucose transport in insulin sensitive tissue.

Hepatic Insulin Resistance

We have seen that basal rate of Hepatic glucose output (HGO) depend on insulin levels which suppresses HGO levels. So the levels of HGO are increased in type 2 DM. The degree of HGO is positively and strongly related to degree of fasting hyperglycemia. This suggests that HGO has a major role in maintaining morning glucose levels. However, if given enough insulin, HGO can be completely suppressed. This is consistent with a decrease in hepatic insulin receptor number.

After meals glucose and insulin enter the liver via the portal circulation and change liver function from glucose producing organ in fasting state to that of storage. Glucose is stored in the form of glycogen but because liver is insensitive to glucose and insulin, there is delayed suppression of HGO suppression in type 2 DM. This is a major contributor to post-prandial hyperglycemia observed in prediabetic and insulin resistance cases.

Peripheral Insulin Resistance

In type 2 DM peripheral insulin resistance is also exhibited in target tissues like skeletal muscles. It is observed that glucose disposal rate is reduced by at least 50% in DM. There is decreased number of insulin receptors, as well as a post binding defect of insulin action.

In normal subjects after cellular uptake, glucose undergoes both oxidative and non-oxidative metabolism. At low insulin levels the pathway of glucose utilization is glucose oxidation (using glucose as a metabolic fuel). At higher insulin conc. glucose is disposed by glycogen synthesis (i.e. glucose is stored). Glycogen synthesis is a major pathway of non-oxidative glucose metabolism. In type 2 DM the efficiency of glucose disposal is reduced by both these processes but primarily by non-oxidative pathway.

Non-Insulin mediated Glucose Uptake

Apart from oxidative and non-oxidative pathways of glucose utilization by insulin independent glucose uptake non-insulin mediated glucose uptake (NIMGU) plays an important role in the rate of glucose disappearance. About 80% of tissue glucose uptake in fasting state occurs via insulin independent mechanisms primarily in CNS and to a much lesser degree in muscles and adipose tissues.

The efficiency of glucose disposal by NIMGU in both normal controls and type 2 DM has been observed to be equal; however the absolute basal rate of NIMGU is higher in type 2 DM which plays an essential role in pathogenesis of DM.

Adipose Tissue

Proteins secreted by adipocytes that act as signaling molecules. Previously adipose tissue was simply regarded as a simple site of fat deposition but now it is regarded as an endocrine gland concerned with release of adipokines or adipo-cytokines. These are potential insulin sensitizers.

(i) Adiponectin (one of the adipokines) acts on skeletal muscles, blood vessels, liver. It causes decreased IC fat and triglycerides. Its levels are decreased in type 2 DM. It positively and strongly correlates with HDL levels.

(ii) Leptin similarly improves glycemic control and is necessary to maintain normal metabolic state.

Obesity, Adipose tissue and Metabolic syndrome

Obesity is increasing in incidence due to imbalance of food intake and energy balance. As body weight increases insulin resistance increases. Dyslipidemia associated with Metabolic Syndrome is strongly related to the higher incidence of insulin resistance. These observations suggest that fat produces a chemical signal that acts on the muscle and liver to increase insulin resistance. Evidence for this includes blocking adipose tissue glucose transporters selectively (GLUT 2). It results in decreased glucose transport in muscles too. One possible signal in fat is FFA which is increased in many insulin resistant states Fat deposits act as endocrine tissues, secreting adipokines some of which decrease and some increase insulin resistance. Leptin and adipokines for example decrease insulin resistance whereas resistin increases insulin resistance.

Adipose tissue now is recognized as a 4th musketeer along with muscles, liver and pancreas.

Causes of Insulin Resistance

(i) Abnormal insulin molecule.

(ii) An excessive amount of circulating antagonist.

(iii) Target tissue defect commonest in type 2 DM- Defects in insulin receptors.

(a) Mutations of receptor gene produce different syndromes associated with defective receptors like:

(i) *Rabson Mendenhall Syndrome*- including tooth, nail, and pineal growth abnormalities.

(ii) *Type A insulin resistance*- In young females with polycystic ovarian syndrome.

(iii) *Presence of antibodies against insulin*- Associated with acanthosis nigricans and other autoimmune phenomenon.

(b) Receptors are rarely abnormal but it is post receptor pathway that is more commonly defective:

(i) There is decreased capacity of GLUT 4 to translocate glucose.

(ii) Defective glycogen synthesis is likely to be present.

(iii) Defective signals- tyrosine kinase.

Intra-abdominal fat is more resistant to insulin than peripheral fat resulting in increased lipolysis and FFA levels, worsening the insulin resistance.

Measurement of Insulin Resistance

HOMA-IR (homeostasis Model Assessment of Insulin Resistance)

$$\text{HOMA-IR} = \frac{\text{Fasting serum insulin x Fasting serum glucose}}{405}$$

1. QUICKI (Quantitative Insulin Sensitivity Check Index)

$$\text{QUICKI} = \frac{1}{\text{Log (fasting serum insulin)} + \text{Log (fasting glucose)}}$$

2. TG / HDL Ratio- greater than 3 is incidence of insulin resistance.

To summarize, there is an increasing incidence of insulin resistance with increasing weight, obesity acting as a main culprit due to imbalance of food intake and energy output. Metabolic Syndrome is associated with dyslipidemia which plays an essential role in increasing insulin resistance especially in muscles and liver.