

## Review Article

# Pathogenesis and Factors associated with Insulin Resistance

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### Abstract

*Insulin resistance has been the subject of much debate over the last two decades. Its pathophysiological basis, however, still remains to be clearly understood. Both genetic and environmental factors have been implicated in its pathogenesis. Mutation of genes encoding signal transduction molecules of insulin and acquired factors like aging, diets, physical activity, obesity and related molecular changes, dyslipidemia, hypertension and smoking were proposed by many groups. This review examined both acquired and genetic factors and discussed model of hormone-receptor-postreceptor interactions to explore the molecular basis of insulin resistance.*

**Key words:** Insulin receptor, Insulin resistance, Dyslipidemia.

### Introduction

The etiopathogenesis of Insulin resistance is a field of extensive research. Insulin resistance attributed to both inherited and acquired factors. Mutations in several genes including insulin receptor substrate-1 (IRS-1) and glycogen synthase gene have been described. Gene mutations so far implicated collectively, however, explain only a small proportion (<5%) of all cases of insulin resistance which suggest that genetically determined insulin resistance is not a dominant cause for the development of type 2 diabetes<sup>1</sup>.

### Results of impaired insulin signaling system in insulin resistance

Impaired insulin signaling results from mutations or post translational modifications of the insulin receptor itself or any of its downstream effector molecules<sup>2</sup>. Evidence suggests that aggravated insulin resistance in T2DM is primarily of a post receptor nature<sup>3</sup>. Insulin receptor tyrosine kinase activity in patients with T2DM is significantly reduced<sup>4</sup>.

### The insulin receptor signaling pathways

There are two major insulin signaling pathways are MAP kinase (Figure I) and PI3-K pathways (Figure II). The heterotetrameric insulin receptor with protein-protein interaction domains involved in insulin signaling<sup>2</sup>. The insulin receptor (Fig I and II) is a transmembrane tyrosine kinase (tyr-kinase) which is widely expressed. It consists of two ligand binding a subunits and two tyr-kinase b subunits that are disulfide linked and form a<sub>2</sub>b<sub>2</sub> heterotetrameric complex<sup>3,5</sup>. Binding of insulin in specific regions of the a subunit generates a signal across the plasma membrane that autophosphorylates the intracellular tyr-kinase domain of the b subunit. This autophosphorylation results in activation of the tyr-kinase activity of the receptor. The catalytic site of the tyr-kinase is occluded by the 'activation loop' in its inactive state which prevents access of ATP and various substrates. Autophosphorylation of tyrosine residues in the activation loop causes a conformational change that allows ATP and substrates to reach the catalytic site<sup>6,7</sup>.

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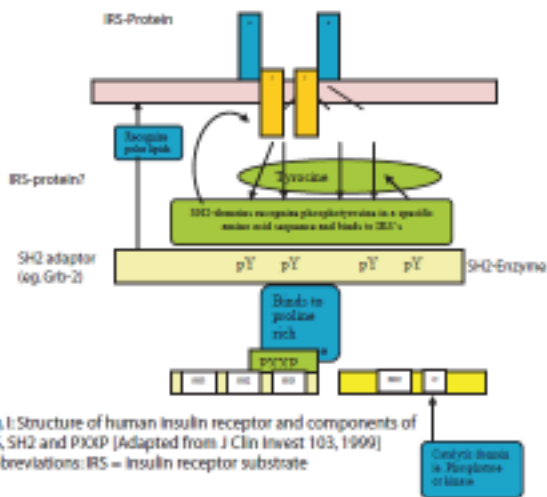
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The activated insulin receptor kinase then phosphorylates substrate proteins at their tyrosine residue and these phosphorylated tyrosine residues in turn serve as docking sites for downstream effectors. Different molecules such as Shc, insulin receptor substrate (IRS) engage the insulin receptor directly and provide a docking interface with downstream substrates<sup>2,8</sup>. IRS proteins contain a conserved pleckstrin homology (PH) domain, located at the NH<sub>2</sub>-terminus that serves to localize the IRS proteins in close proximity to the receptor<sup>9</sup>.



**Figure-I:** Structure of human insulin receptor and components of IRS, SH2 and PXXP [Adapted from J Clin Invest 103, 1999] Abbreviations: IRS=insulin receptor substrate.



**Figure-II:** Insulin receptor, components of the mitogen activated (MAP) kinase and phosphatidylinositol 3 kinase (p13-K) signaling pathways, and insulin actions<sup>42</sup> [Adapted from Diab Care 24: 2001] IRS

proteins also contain a PTB (phosphate tyrosine binding) domain COOH-terminal to their PH domain which recognizes the phosphotyrosine in the amino acid sequence asparagine-protein-anyamino acid-phosphotyrosine (NPXPY). The PTB domain which is present in a number of signaling molecules<sup>10</sup> shares 75% sequence identity between IRS-1 and IRS-2 and functions as a binding site to the NPXY amino acid motif of the juxtamembrane region of the insulin receptor to promote IR/IRS-1 interactions. The COOH-terminal region of IRS proteins contains multiple tyrosine phosphorylation motifs that serve as docking sites for proteins which mediate the metabolic and growth promoting functions of insulin.

Insulin receptor signaling (Fig I and II) involves two major pathways, i.e., the (MAP) kinase and the PI3 kinase. Each of these two pathways under certain circumstances can activate the other. Thus, Akt (protein Ser/Thr kinase B) may activate Raf kinase and conversely Ras may activate PI3-K42. The metabolic response to insulin is primarily mediated via the PI3-K pathway.

Nuclear transport of signaling molecules: Signaling substrates of the Tyr-kinase receptors can be grouped into three levels (Fig. II) depending on their proximity to the receptor.

Level-1: The proximal substrates e.g. IRS proteins and SHC and the proteins that directly interact with them.

Level-2: Downstream intermediates e.g. MAP kinases, Akt and related substrates.

Level-3: Molecules that affect the final biological responses e.g. Gsk3, aPKC

Level-1 and level-2 molecules function primarily at the plasma membrane or in the cytosol. On the other hand, many of level-3 molecules are transported into the nucleus because their specific function involves the regulation of gene transcription<sup>11</sup>.

Insulin enhances glycogen synthesis. Glycogen synthase kinase-3 (GSK-3) mediates the activation of glycogen synthase in response to insulin. Activation of Akt by insulin causes in the phosphorylation and inactivation of GSK-3, making it incapable of inhibiting glycogen synthase activity. GSK-3 also inactivates the protein synthesis eukaryotic initiation factor (eIF)-2B by phosphorylation. Insulin enhances protein synthesis by inactivating GSK-3 via activated Akt<sup>12</sup>. Insulin also activates protein synthesis at the translational level by phosphorylation of p70S6 kinase and 4E-BP1 via

the kinase mammalian Target of Rapamycin mTOR. It is also reported that all types of dyslipidemia have relations with insulin resistance<sup>13</sup>. These interactions need so broad discussion that is beyond the limit of present article. A separate review article is needed for this.

## Environmental factors

Environmental factors implicated in the development of insulin resistance include: 1) aging, 2) dietary constituents, 3) level of physical inactivity, 4) pregnancy, 5) obesity and 6) hypertension and 7) smoking.

**Aging:** It is argued that insulin sensitivity decreases with age since (i) advancement of age showed association with changes in body composition, i.e. loss of muscle mass and increase in fat deposition which cause reduction of active metabolic tissue; ii) change in lifestyle (diet and physical activity); iii) neuro-hormonal variation; and iv) increased oxidative stress<sup>14-19</sup>. However, healthy centenarians found to have a preserved insulin action compared to aged subjects<sup>19</sup>, in healthy Europeans, age per se is not a significant cause of insulin resistance<sup>15</sup>. Age related deterioration in glycemic dysregulation suggested to be resulting from decrease in beta cell function without change in insulin sensitivity<sup>20</sup>.

**Dietary constituents:** Dietary constituents are known to influence insulin sensitivity. Individuals often accustomed to diet rich in calorie. It is known that choice of food attributed to socio-cultural factors. In case of diet habit of rich food excess calorie is deposited as fat giving rise to chance of obesity. Diet containing high fat, low fibers and more refined carbohydrates tend to reduce insulin sensitivity<sup>21</sup>. It is not only calorie value of food counts rather dietary fibers and trace elements are also of great importance. Dietary fibers play important role in dynamics of absorption from the intestine. Trace elements play critical role as cofactors of different enzymes. So far magnesium and selenium found to have important influence on insulin sensitivity<sup>22,23</sup>.

**Exercise:** Physical activity found to improve insulin sensitivity<sup>24</sup>. Short term low intensity exercise reduces insulin resistance without affecting BMI<sup>25</sup> although it does not affect insulin secretion. The underlying mechanism of exercise to reduce insulin resistance is yet to fully understood, however, it have been proposed that exercise causes increase in insulin induced glucose

uptake and subsequently increased glycogen synthesis activity in skeletal muscle<sup>1</sup>. It was also suggested that exercise causes contraction-induced increase in GLUT-4 content in skeletal muscle. Acute exercise also enhances insulin stimulated GLUT-4 translocation<sup>26-28</sup>. Exercise also found to reduce triglyceride levels and improve insulin sensitivity. However, the effect of exercise on insulin sensitivity is transient and disappears after 17-19 days on discontinuation<sup>29</sup>.

**Pregnancy:** Women with pregnancy both obese and non-obese were reported to develop insulin resistance during third trimester<sup>30</sup>. The mechanism of development of this insulin insensitivity has, however, not yet fully elucidated. Although from metabolic point of view pregnancy was claimed to be a state of accelerated starvation<sup>31</sup>. In early part of gestation maternal fat deposition was reported and possibly owing to effects of lipolytic hormones e.g. human placental lactogen and human chorion gonadotropin<sup>1</sup> plasma free fatty acids level rise during later part of pregnancy and might be other plausible factors accentuating the insensitivity if insulin which are yet to be identified.

**Obesity:** Obesity is reported to be one of the strongest predictors of low insulin sensitivity. For each kilogram of weight gain, the risk of diabetes increases between 4.5% and 9%<sup>1,32</sup>. Insulin resistance increases with weight gain and decreases with weight loss; indicating insulin resistance related to obesity is a reversible condition. Causes of insulin resistance in obesity are not fully understood. It is hypothesized that the expanding adipose tissue of the obese individuals may produce compounds that are either released into the bloodstream and cause insulin resistance in remote targets (e.g. in skeletal muscle or liver), or in close vicinity of target organs acting through paracrine mechanisms<sup>33</sup>. Among these secreted compounds are: 1) Tumour necrosis factor alpha (TNF), 2) free fatty acids (FFA), 3) leptin, 4) resistin and 5) adiponectin.

TNF $\alpha$ - TNF $\alpha$  is over expressed in adipose tissue of obese insulin resistant rodents and humans, and has been shown to produce insulin resistance in isolated cell systems<sup>34</sup>. However, several others have suggested TNF $\alpha$  to be unlikely contributor in the development of insulin resistance associated with obesity<sup>35, 36</sup>. FFAs - There are many evidences which show that FFAs are an important link between obesity and insulin resistance<sup>33,37,38</sup>. Location of the FFAs induced defect may be either at the level of ISGU or glucose phosphorylation or an inhibition of carbohydrate oxidation<sup>39,37</sup>.

Rates of ISGU, glycogen synthesis and glycolysis all were found to reduce in the presences of higher blood FFAs levels. Increasing plasma FFAs was associated with an acute increase in intramyocellular triglyceride (IMCL-TG) and 40% increase in insulin resistance. IMCL-TG is a metabolically active pool of fat consisting of small oil droplets located in close proximity to mitochondria providing fuel<sup>1</sup>.

Leptin - Leptin was identified<sup>40</sup> as an adipocyte derived hormone and found to reduce body weight via specific receptors in hypothalamic areas regulating energy expenditure and satiety. Leptin deficiency and receptor defects in rodents found to cause marked obesity as well as hyperinsulinaemia and hyperglycaemia. Number of studies has focused on the effects of leptin on insulin resistance and insulin secretion. Both inhibition and stimulation of insulin action have been shown by leptin in different cell systems. Therefore, the conclusion that leptin causes a defect in the insulin signaling chain or that it is capable of improving  $\beta$ -cell dysfunction in human subjects cannot yet be made on the basis of these studies<sup>41</sup>.

Resistin - Resistin is a protein released from white adipose tissue of mice which can cause insulin resistance<sup>42</sup>. However, whether it plays a role in human physiology is still unclear.

Adiponectin - It is also a protein released from adipose tissue which has been reported to have potential role in the determination of insulin sensitivity. It is more strongly inversely related with intra abdominal than subcutaneous fat<sup>43,44</sup>. Though some recent studies have shown that it was not BMI but the quantity of intra-abdominal fat was strongly related to insulin sensitivity<sup>45</sup>.

**Hypertension:** Studies show that there is significant relationship between plasma insulin level and both diastolic and systolic blood pressure in both obese and non-obese subjects<sup>46-48</sup>.

**Smoking:** Smoking is reported to reduce serum HDL-Cholesterol levels and increase serum triglyceride levels both of which causes diminution of insulin sensitivity. Moreover, a number of medications including corticosteroids<sup>49</sup> and growth hormone<sup>50</sup> have been shown to induce insulin resistance.

## Conclusion

Insulin resistance is the result of interactions of genetic and acquired causes. Effective measures to ameliorate

the common factors (Environmental factors in particular) may help prevent the possible chance of developing the insulin resistant and its related conditions and improve the situation apart from already established phenomena.

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