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REVIEW ARTICLE

Pathophysiology of Insulin Resistance

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Introduction

Insulin resistance is the reduced ability of insulin to perform its normal physiological functions, and hence greater than normal amount of insulin is eventually required to obtain a quantitatively normal biological response[1].The clinical importance of insulin resistance was recognized after the discovery of the insulin action at the cellular level, many decades ago. Himsworth and Kerr first described insulin resistance in nineteen forties[2], but their ideas finally got a confirmation after raised insulin levels were first assessed in diabetics by Radio Immuno Assay by Berson and Yalow[3], a fact which was also endorsed by Roth and Reaven[4] in their numerous works. Being a key regulator of glucose homeostasis, insulin resistance leads to impaired glucose tolerance followed by development of diabetes[5].Insulin also affects lipid and protein metabolism, contributing to various metabolic abnormalities associated with the metabolic syndrome as described by Reaven[6]. As Insulin has numerous metabolic, vascular and other actions, resistance can thus develop to all aspects of insulin action.

Atherosclerosis, the main culprit behind the macro-vascular diabetes complications such as coronary artery disease (CAD), peripheral vascular disease (PVD) and stroke, has been linked to insulin resistance and hyperglycemia, thus contributing to an increased risk of CVD and heart failure both in diabetic as well as non-diabetic individuals. Insulin resistance and compensatory hyperinsulinemia are common in patients of essential hypertension, though not all hypertensive individuals may be insulin resistant [Reaven G 2003]. Various clinical studies have demonstrated that hyperinsulinemia or glucose intolerance is present in almost 50% of hypertensives, whereas upto 80% of type 2 diabetic patients have hypertension. Recent data has shown that besides the classical insulin- responsive tissues, insulin resistance also develops in cardiovascular tissues where it contributes to the development of hypertension as well as cardiovascular disease.

Cellular Mechanisms of Insulin Resistance

Understanding of the pathophysiology of insulin resistance and consequent diabetes has undergone quite a few interesting turnovers in the last one decade. We are well aware of the fact that derangements in three organ systems- namely the liver, pancreatic β cells and the peripheral target tissues- skeletal muscle and adipose tissue- conspire together to produce abnormalities in glucose and lipid metabolism, leading to insulin resistance and eventually type 2 diabetes[7]. Numerous studies have charted out the roadmap of diabetes progression over a continuum of worsening insulin action, which starts with peripheral insulin resistance and eventually ends with a loss of insulin secretion. Insulin resistance develops much earlier than the appearance of dysglycemia, and is generally associated with obesity and a sedentary lifestyle, ageing as well as

a genetic predisposition. Though there is still confusion over the identification of the primary lesion and the relative contribution of the different tissues implicated, they all contribute to the syndrome[8]. The β cells normally compensate for this resistance by increasing both basal and prandial insulin secretion to maintain normal glucose levels. Eventually, this compensation fails, leading to development of glucose intolerance and then frank diabetes, which further worsens with increasing insulin resistance[9].This combination of impaired insulin action in peripheral tissues and β cell function leads to increase in the hepatic gluconeogenesis, leading to numerous tissue abnormalities, the diabetes " ruling triumvirate" by De Fronzo [7].

But, this view becomes paradoxical because on the one side insulin resistance is occurring primarily in the muscle and fat, but we say that diabetes per se is mainly a disease of the β cell and the liver that actually are not the primary targets of insulin resistance. Off late experimental studies involving targeted mutagenesis in mice have lead to a need for reassessing of the primary site of insulin resistance. Mice that had peripheral resistance to insulin action developed impaired glucose tolerance, but did not become diabetic, and their β cell function was conserved all through their life[10]. So, till insulin action in liver is preserved and β cell strain is absent, these mice can overcome peripheral insulin resistance. Mice with selectively impaired insulin signalling in the muscle demonstrated only a mild impairment in glucose metabolism without any marked insulin resistance systemically[11]. This lead to the recognition of alternate biochemical pathways that could bypass insulin signalling to cause glucose utilisation in muscle (namely through the IGF1 receptor and the contraction-activated pathway). We also know that there is an early development of insulin resistance and dysglycemia when insulin sensitive GLUT-4 glucose transporter in the muscle is selectively disrupted causing a profound decrease in both insulin- as well as contraction- stimulated glucose transport[12]. Also, alterations in the insulin regulated hepatic [13] and β cell gene expression and β cell neogenesis have now been recognised as very important contributors to the pathogenesis of type 2 diabetes.

These studies thus exhibited that, inactivation of insulin signalling in tissues such as muscle and fat that exhibit insulin- dependent glucose uptake and utilization, results in milder degrees of dysglycemia[14] whereas in tissues such as the brain, liver and β cells that are non-insulin dependent, inactivation of insulin signalling is associated with significant metabolic abnormalities, suggesting a primary role of these tissues in insulin resistance[15]. Additional data have suggested a direct role of insulin signalling in beta cell function and regulation of beta cell mass[16].

Role of Genetics in Insulin Resistance

Insulin resistance in many individuals is determined genetically. Having a first degree relative with T2DM increases a 25% lifetime risk of getting the disease. Also the concordance rate for T2DM in monozygotic twins outnumbers that of the dizygotic twins, suggesting that genes are responsible for this variation[17] .Various studies of monogenic forms of insulin resistant diabetes [18] have revealed a wide range of diabetes susceptibility genes, inspite of various other confounding factors such as environment (diet, sedentary lifestyle), genetic heterogeneity and polygenic inheritance.

Insulin Resistance and Cardiovascular Disease

Insulin resistance is associated with both atherosclerosis as well as CAD in both diabetic as well as non- diabetic individuals, with fasting serum insulin levels showing an association with cardiovascular disease independent of other risk factors. Even in type 1 diabetes, high insulin doses and weight gain over time is often associated with an elevation in the risk for CVD more so in the background of a positive family history showing a gradual development and worsening of insulin resistance. Insulin resistance demonstrably has been shown to predict the extent of coronary calcification independent of blood glucose levels in type 1 diabetes, highlighting its contribution to CVD even in type 1 diabetics.

In contrast, in type 2 diabetes, insulin resistance does not worsen when hyperglycemia develops, rather it is the progressive decline in insulin secretion by the pancreas that fails to compensate for the insulin resistance in the skeletal muscle, liver and adipose tissue that causes further worsening of glycemia and an increase in the risk of CV complications even in pre-diabetes.

Defects in Insulin Action on Glucose Metabolism

Liver: Insulin resistance contributes to an increase in endogenous hepatic glucose production (HGP), showing a significant relationship between fasting plasma glucose (FPG) concentration and HGP in T2DM[19]. After a meal, the increase in insulin and glucose concentrations

and a concomitant reduction in glucagon normally causes a complete suppression of the endogenous glucose production. This suppression is inadequate in insulin resistance. Studies by Reaven[20] and Beck Nielsen[21] have demonstrated that HGP is only mildly raised in diabetic patients compared to normoglycemic individuals. Thus an inadequate suppression of HGP can be a major reason for post-prandial hyperglycemia as a consequence of the liver's resistance to insulin action, and the inability of glucose itself to normally suppress hepatic glucose output. The degree of hepatic insulin resistance appears to be closely related to the amount of fat deposited in the liver, independent of overall obesity.

Skeletal Muscle: As the major site of glucose utilization in most of the infusion studies is the skeletal muscle[22], it can be easily deduced that a defective glucose uptake at the muscle could be an important contributor to diabetes. But the fact that a similar defect also occurs in first degree relatives of type 2 diabetics who are normoglycemic[23] and independent of obesity indicates that this defect, by itself, cannot be responsible for the development of significant hyperglycemia in T2DM. Thus there is either an additional genetic defect or myocellular metabolic disturbances such as glucotoxicity or lipotoxicity could be responsible for this, as intramyocellular lipid content has also been seen to be higher in type2 diabetics[24].

Defects in Insulin Action on Lipid Metabolism

Adipose Tissue: Adipose tissue is very sensitive to insulin and it has been demonstrated that there is half- maximal suppression of plasma free fatty acids (FFA) at a serum insulin concentration of around 20 μU/ml[25]. Thus even minor variations in insulin concentrations can have major effects on plasma FFA levels. Also, ambient plasma FFA levels are higher than normal in type 2 diabetics-greater the plasma FFA concentration, greater is the plasma glucose level[26].

When insulin resistant individuals fail to maintain a state of compensatory hyperinsulinemia, there occurs a rise in plasma FFA levels, leading to the development of significant hyperglycemia. This could occur because of increased FFA transport to the liver secondary to their increased serum concentrations, stimulating FFA oxidation and increased hepatic neoglucogenesis[27] .Also insulin-stimulated glucose uptake is reduced with rise in plasma FFA concentration. This marked rise in plasma FFA and glucose levels further compromises the β cell secretory function[28]. This decline in insulin secretion would further increase FFA concentration, reduce muscle glucose uptake, raise hepatic FFA oxidation and increase gluconeogenesis, further compromising β cell function and worsening the hyperglycemia.

Defects in Lipoprotein Metabolism and Ensuing Dyslipidemia

Resistance to insulin mediated glucose uptake and subsequent compensatory hyperinsulinemia also cause secretion of Very Low Density Lipoprotein-Triglyceride (VLDL-TG) secretion in the liver and hypertriglyceridemia. Insulin normally suppresses VLDL production from the liver not only by reducing NEFA availability by inhibiting lipolysis in the adipose tissue but also by direct inhibition of the assembly and production of VLDL particles in the liver. A failure of this suppression of VLDL apoB production, subsequently raises the TG concentration in type2 diabetics[29]. Hypertriglyceridemic conditions provide an excessive time for cholesterol ester transfer protein (CETP) mediated exchange of cholesterol esters and TGs between the HDL and expanded pool of TG-rich lipoproteins. Thus HDL particles get enriched with TG forming an easy substrate for hepatic lipase, thus reducing HDL levels in such insulin resistant individuals. There is also an increase in the CETP-mediated exchange of cholesterol ester and TG between VLDL and LDL particles secondary to an increase in VLDL levels, which increases the TG content of the LDL particles, making them a better substrate for hepatic lipase which hydrolyses the TG in the LDL particle, reducing their size. This causes an increase in the small dense LDL particle concentration which are highly atherogenic thus providing a plausible relationship between insulin resistance and cardiovascular disease[30] as well as affecting the endothelial and arterial function.

Role of Obesity and Physical Activity

Obesity is an important contributor, though not an essential pre-requisite[31] to the development of insulin resistance by reducing insulin- stimulated glucose uptake. This may be facilitated by a number of mediators released from adipose tissue such as elevated levels of FFAs, TNF-α, leptin, resistin, adipsin, amylin as well as tissue accumulation of lipid. The correlation between insulin resistance and obesity is evident across all ethnic groups and across the full range of body weights. Studies have revealed that insulin resistance rises with increase in body fat content, represented by body mass index BMI[32]. Central (intra-abdominal) obesity is much more strongly related to insulin

resistance, type 2 diabetes and cardiovascular disease than the peripheral (gluteal/ subcutaneous) obesity[33].

A demographic variation is seen in the relative contribution of insulin resistance and impaired beta cell function in the causation of T2DM. Asian Americans, though relatively less obese than the Native Americans are seen to be much more insulin resistant due to their higher visceral fat accumulation. South Asian ethnic populations (India, Pakistan, Bangladesh) have been shown to have a much higher degree of abdominal fat mass at the same degree of total fat mass than Caucasians, thus increasing their risk for cardiovascular disease manifold. Though the relative contribution of adipose tissue insulin resistance to whole body glucose disposal is as low as around 10%, it has a major role in obesity- related insulin resistance. Expression of pro-inflammatory cytokines from the hypertrophied adipocytes along with macrophage accumulation contributes to adipose tissue insulin resistance, manifesting as reduced suppression of lipolysis leading to influx of FFAs to the liver and skeletal muscle, thus aggravating peripheral insulin resistance. Ectopic fat deposits in organs such as liver, muscles and blood vessels cause activation of tissue leucocytes in organ systems, further exacerbating systemic insulin resistance.

Weight loss has been shown in obese individuals to have improved insulin sensitivity[34].Exercise and increased physical training also enhances insulin sensitivity, reduces plasma insulin and TG levels, reduces blood pressure and increases HDL levels[35].

Implications of Insulin Resistance

The impact of insulin resistance and its numerous metabolic consequences have wide implications for human disease such as the development of T2DM, obesity, hypertension, dyslipidemia, cardiovascular atherosclerotic diseases as well as various other pathological and physiological states [36]. The potent admixture of insulin resistance and compensatory hyperinsulinemia predisposes to the development of an array of abnormalities comprising the metabolic syndrome. It has been also linked to enhanced renal sodium retention and sympathetic vascular tone causing hypertension, hyperuricemia [37], dysfibrinolysis and raised PAI-1 levels [38], resting tachycardia[39] and polycystic ovarian syndrome[40] along with dyslipidemia. Insulin resistance is thus increasingly being assessed and studied as a key player in the aetiopathogenesis and consequences of these various clinical states, markedly increasing the risk of T2DM and cardiovascular disease.

Conclusion

Insulin resistance in peripheral tissues develops much earlier than the onset of hyperglycemia. As long as the insulin resistant individuals are able to increase their insulin secretion to compensate for this, major dysregulation of glucose homeostasis does not occur and normoglycemia can be maintained with this compensatory hyperinsulinemia. When this compensatory insulin secretory response declines to a level where there is a marked elevation in the plasma FFA concentration due to increased lipolysis. There is a precipitous rise in plasma glucose levels due to inadequate suppression of hepatic neoglucogenesis leading to marked hyperglycemia and T2DM.

Defects in all the organ systems – peripheral target tissues – the muscle and fat as well as the liver and pancreatic β cells- all are important contributors to the pathogenesis of insulin resistance and type 2 diabetes, each having their own significant role in its evolution , against a conducive background of environmental and genetic factors. This has lead to proposal by Domenico Accili of "replacing the original picture of the ruling triumvirate with that of a squabbling republic in which every tissue contributes to the onset of the disease"[41].

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"A wise man should consider that health is the greatest of human blessings, and learn how by his own thought to derive from his illnesses."

— Hippocrates