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Review Article

Relation between Type 2 Diabetes and obesity: A review

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Abstract

The aim of this article was to review the relationship between type 2 diabetes and obesity. The most important environmental risk factors in most patients who develop type 2 diabetes were high caloric intake, decreased physical activity, family history and stronger multiple genetic predisposition. Obesity induces insulin resistance and its mechanism is poorly understood. Inflammation may be the common mediator linking obesity to the pathogenesis of diabetes.

Keywords: Type 2 Diabetes, Obesity, Insulin resistance, Inflammation

1. Introduction

Diabetes mellitus (DM) and obesity have a complex relationship, with type 2 diabetes strongly associated with obesity. It is a common disorder known to everybody nowadays, with a prevalence that rises markedly with increasing degrees of obesity[1]. The prevalence of type 2 diabetes is rising in the past decade[2]. and is mostly associated with obesity3. The characteristic of obesity is Insulin resistance with hyperinsulinemia and is present before the onset of hyperglycemia. Once the obesity comes, the first and foremost observable changes are impaired glucose tolerance and increased insulin resistance, which result in hyperinsulinemia. This might be results from a combination of multiple genetic predisposition and environmental factors, that makes deranged insulin secretion.

2. Pathophysiology

The pathogenesis of Type 2 Diabetes mellitus is characterized by decrease in beta cell secretion of insulin or a decrease response of the tissues to respond to insulin, i.e. insulin resistance. The main factor involved in the pathogenesis of type 2 DM is environmental factor. Obesity is one of the most important causes although genetic predisposition is also important which causes deranged insulin secretion and cause hyperglycemia. This hyperglycemia causes beta cell exhaustion and decrease in insulin secretion. Other metabolic disturbances cause reduced responsiveness of tissues to insulin action called as insulin resistance. It is a major factor in the development of type 2 DM.

Pathogenesis of Type 2 Diabetes

Genetic predisposition --------- Insulin resistance ----- Environmental factors
(Obesity, Sedentary life, aging)

↓

Hyperinsulinemia

↓

Impaired glucose tolerance

Impaired glucose tolerance

↓

Genetics --------- Beta – Cell – failure ---------- Acquired conditions

(glucotoxicity, increased FFA, others)

Increased
Hepatic glucose
output ----------

↓

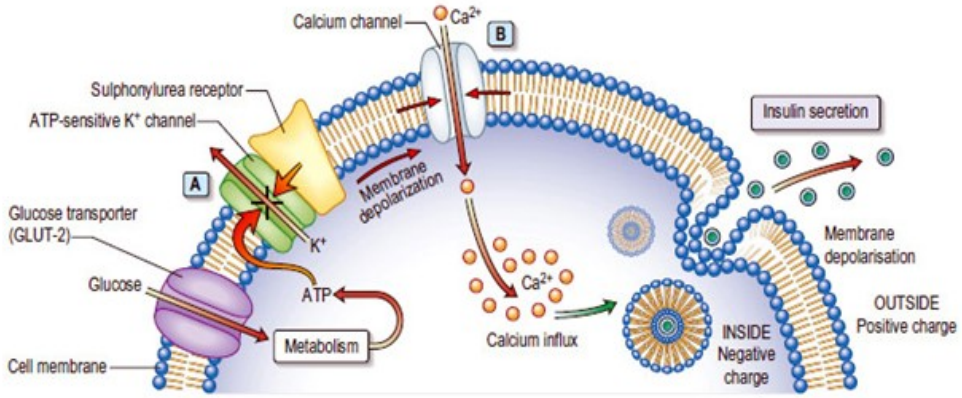
Type 2 diabetes

Type 2 diabetes is mostly accompanied by other conditions, including hypertension (140/90 mmHg), high serum low-density-lipoprotein (LDL) cholesterol concentrations, and low serum high-density-lipoprotein (HDL) cholesterol (= 35 mg/dl), that results into increase in cardiovascular risk. The clinical condition is called as metabolic syndrome[4]. Hyperinsulinemia results in response to insulin resistance may play an important role in the genesis of these abnormalities. Increased free fatty acid levels, inflammatory cytokines from fat, and oxidative factors, together all plays a major role in the pathogenesis of metabolic syndrome, type 2 diabetes, and their risk factors.

2.1 Insulin secretion

For the secretion of insulin, beta cells requires a transporter into the cell known as Glucose transporter 2(GLUT-2), phosphorylated by an enzyme glucokinase. One study in mouse found that genetic alteration in GLUT2 expression will produce insulin resistance[5]; similar genetic alteration at GLUT-2 could be induced in a normal mice fed a high fat diet and this concludes that a possible link between high fat diet and development of diabetes[6].

Fig 1: Insulin Secretion



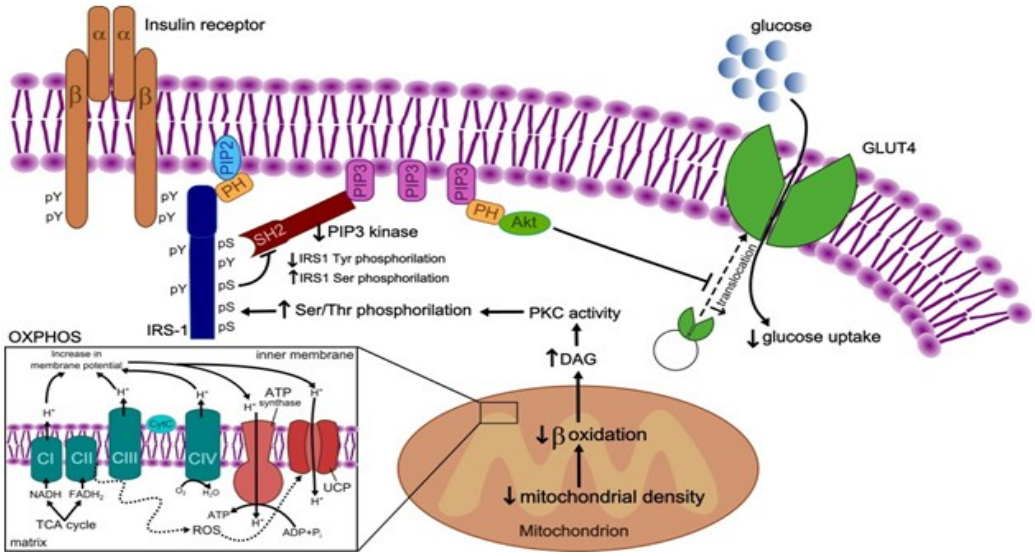
2.3 Insulin resistance

Insulin resistance is the major factor in the development of type 2 diabetes[7,8]. The majority of the people with type 2 DM have multiple genetic defects. Insulin resistance is usually be related with substances secreted by adipocytes ("adipokines" including leptin, adiponectin, tumor necrosis factor alpha, and resistin). The importance of the combination of genetic and environmental factors is suggested by another study of nondiabetic offspring of two parents with type 2 diabetes[8]. Their insulin sensitivity was similar to that of normal subjects with no family history of type 2 diabetes at similar BMI; but with increasing degree of obesity, insulin resistance increases in those with a family history of type 2 diabetes[8].

2.4 Insulin Action

Insulin acts on respective tissues by first passing through the circulatory system, binds to specific receptor known as beta–3–adrenergic receptor in target tissues. The intrinsic protein tyrosine kinase activity is essential for insulin receptor function. Rapid receptor autophosphorylation and tyrosine phosphorylation of cellular substrates (e.g., insulin receptor substrates 1 and 2) are important early steps in insulin action. Thereafter, a series of phosphorylation and dephosphorylation reactions are triggered that ultimately produce insulin's effects in insulin-sensitive tissues (liver, muscle, and fat). The receptor regulates lipolytic effect on various visceral organs and increases the thermogenesis in the tissues. A low metabolic activity, high risk of obesity, and the early onset of type 2 diabetes is the initial observation[9, 10] found in the receptor due to the sudden mutation in the gene. A variety of post-receptor signal transduction pathways are activated by insulin, including PI3 (phosphatidylinositol 3) kinase, an enzyme that appears to be critical for the translocation of glucose transporters (GLUT 4) to the cell surface and, in turn, glucose uptake.

Fig 2: Mechanism of Insulin action



2.5 Obesity and Inflammation

For example obesity, causes peripheral resistance to insulin-mediated glucose uptake and hence the glucose uptake by the cells is decreased and utilization of the glucose by the cells decreased and this is because of lost of sensitivity of the beta-cells to glucose on the cells[11]. The significant results of these are reversed by weight loss, leading to a decreased blood glucose levels towards normal.

The mechanism by which how obesity causes insulin resistance are poorly understood. The fat distribution and may be a genetic abnormality in the beta-3-adrenergic receptor, contribute a major role. Studies shows that an c-Jun amino-terminal kinase (JNK) pathway may be an important mediator of the how the obesity causes insulin resistance that leads to increased JNK activity and further leads to increased in obesity, and this is a consequence that interfere with insulin action.

Many studies have shown that inflammation is the common mediator linking the obesity to the pathogenesis of diabetes and atherosclerosis[12,13] .The incidence of type 2 diabetes along with that, results in increased levels of markers of inflammation, including C reactive protein, IL-6, plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor (TNF)-alpha, and white cell count[14-17] is seen .

2.6 Free fatty acids

Usually in obesity persons, plasma FFA levels are high. Sudden increased levels of FFA is a major risk factor for type 2 diabetes (relative risk 2.3)[18], may inhibit insulin secretion and can inhibit insulin-stimulated glucose uptake and utilization by the cells in patients with type 2 diabetes[19].

Increased plasma FFA in obese persons may inhibit insulin secretion and blocks glucose supply in patients' with

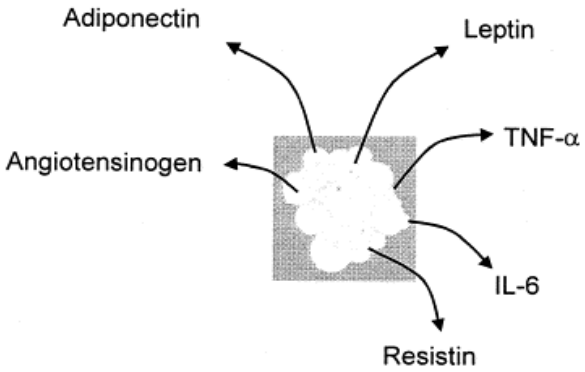
Type 2 diabetes. Increased plasma FFA in obese persons also causes the cytokine damage, a substance derived from adipose tissue, that leads damage of cytokine-induced organs.

3. Role of Adipokines

3.1 Leptin

Leptin is secreted by adipocyte and its secretion depends upon adipocyte mass. It gives information about the quantity of stored fat to hypothalamus. Various studies in humans and animals have shown that leptin deficiency and leptin resistance are associated with obesity and insulin resistance.

Fig 3: Release of adipokines from adipocytes



3. 2 Adiponectin

Adiponectin is secreted from an adipocytes tissue, reduces the levels of blood free fatty acids and has been associated with improved lipid profiles, better glycemic control, and reduced inflammation in diabetic patients[20]. Several studies shown that Adiponectin is having inhibitory effect on insulin resistance and hence deficiency of Adiponectin is having stimulatory effect on insulin resistance and causes development of type 2 diabetes21. Apart from these visfatn, and vaspin also having an inhibitory effect on insulin resistance.

3. 3 Tumor necrosis factor-alpha

TNF-alpha (TNFa) from adipose tissue may play a major role in stimulating the insulin resistance[22-25].

FFA in obesity, that leads to fatty acid toxicity are responsible for increased expression of TNFa in obesity. This is due to because of a fatty acid-binding protein in adipocytes, aP2, which provides the link by which FFA in obesity leads to increased expression of TNFa in obesity.

A preliminary study has been done and shown a strong correlation between the degree of obesity, hyperinsulinemia, and TNFa mRNA in adipose tissue. In addition to that, in a study of a homogeneous Native Canadian population, plasma TNFa levels were positively correlated with increased insulin resistance[26].

4. Role of Chemokine molecules

The chemokine molecule CXCL5 (CXC ligand 5) are present at high levels in the macrophage fraction of white adipose tissue[27]. When it binds to the chemokine receptor CXCR2, it reduces insulin-stimulated glucose uptake in muscle and suggesting a vital role of CXCL5 in developing insulin resistance.

4.1 Plasminogen activator inhibitor

Plasminogen activator inhibitor 1, an inhibitor of fibrinolysis, is another protein secreted from adipocytes. High levels of plasminogen activator inhibitor 1 are an prior indicator of onset of diabetes. Other adipocytokines, including adiponectin, tumor necrosis factor alpha, and leptin, are not independently prior predict of diabetes.

4.2 Resistin

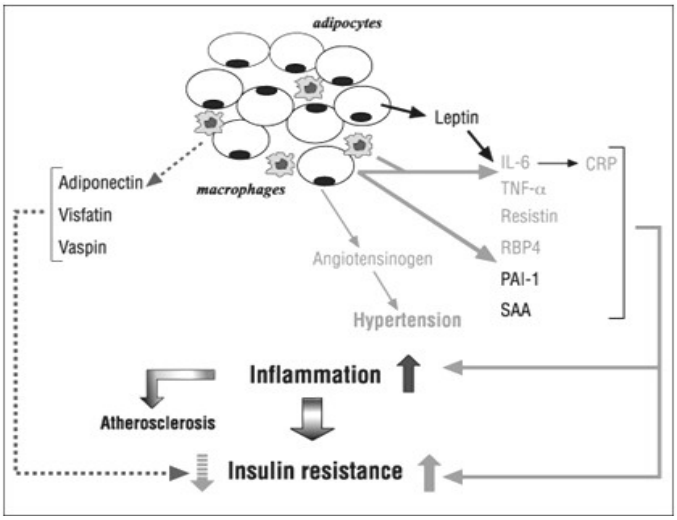
Resistin stimulates the insulin resistance and decreases glucose uptake and utilisation by the adipocytes 28, 29.

Thus, resistin may be a hormone that links obesity and leads to development of type 2 diabetes.

4.3 Interleukin-1 beta

Another cytokine, interleukin-1 beta, an inhibitor of glucose-induced insulin secretion, has been reported to undergo increased synthesis by the islets of the beta cells under situations of high glucose levels[30]. Chronic exposure to hyperglycemia leads to high levels of interleukin-1-beta within the islet destroys beta cell function.

Fig 4: Factors affecting on Insulin resistance



The above diagram showing the factors which will decrease and increase the insulin resistance. Adipokines such as Adiponectin, visfatin, and vaspin are having an inhibitory effect on insulin resistance, whereas adipokines such as leptin, IL-6, TNF-alpha, resistin and all these factors are involved in stimulating the insulin resistance, which plays a major role in the development of type 2 diabetes mellitus.

5. Conclusion

Type 2 diabetes mellitus is caused by a combination of varying degrees of insulin resistance and relative insulin deficiency which is brought by multiple genetic predispositions and environmental factors. Current research focuses upon genes encoding for proteins that might be involved in pancreatic development, insulin synthesis, secretion, or action. Increased weight gain and decreased physical activity are the common environmental risk factors for development of Type 2 diabetes. The mechanism by which obesity induces insulin resistance is poorly understood. Inflammation may be the common mediator linking obesity to the pathogenesis of diabetes. Visceral obesity plays an important role in the development of diabetes by mobilizing free fatty acids and certain inflammatory cytokines promoting insulin resistance. Adiponectin which is secreted from adipose tissues is inversely correlated with weight gain. We recommend further studies to understand the molecular mechanism of obesity for insulin resistance and diabetes in different populations, since genetic predisposition plays an important role in the pathogenesis of insulin resistance.

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