Relation between Obesity, Insulin Resistance and T2DM: Review Article

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Abstract

Obesity considered as a serious epidemic and one of the leading global causes of preventable deaths. The prevalence of obesity and diabetes mellitus (DM) has been consistently increasing worldwide. There is a strong link between obesity and insulin resistance (IR), as in more than 80 % of patients with obesity develop IR at specific points in their lifetime, which eventually predisposes to metabolic disorders, including metabolic syndrome, prediabetes and T2DM. Sharing powerful genetic and environmental features in their pathogenesis, obesity amplifies the impact of genetic susceptibility and environmental factors on DM. This study aimed to review relation between obesity, insulin resistance and T2DM.

Key words: Body mass index, Diabetes mellites, HOMAIR.

Introduction

One of the main preventable causes of death worldwide and a major epidemic is obesity. The primary cause of the growing type 2 diabetes mellitus (T2DM) epidemic worldwide is the increased incidence of obesity. Because obesity and type 2 diabetes are directly correlated, studies found that individuals with body mass index (BMI) values between 25 and 29.9 kg/m^2 had a 2% increased chance of having diabetes, and those with BMI values over 35 kg/m^2 have a roughly 13% increased risk (1)**.**

T2DM accounts for about 96% of diabetes mellitus cases. According to the global burden of diabetes study, 529 million people globally had diabetes in 2021, and more than 1.31 billion people are predicted to have the disease by 2050 (2)**.**

Patients with type 2 diabetes have a 15% higher mortality risk than those without the disease, and the main cause of morbidity and death linked to T2DM is cardiovascular disease (3).

The management of obesity has been shown to be able to slow the progression from prediabetes to type 2 diabetes. Sustained weight loss has also been demonstrated to enhance glycaemic control and lessen the requirement for glucose-lowering drugs in overweight or obese T2DM patients (4).

Aim of the study

In this study, we aimed to review the relation between Obesity, Insulin resistance and T2DM to early detection, diagnosis and management of T2DM.

Obesity

American diabetic association (ADA) defined obesity as a chronic and often progressive disease with numerous medical, physical, and psychosocial complications, with a substantially increased risk for T2DM. According to BMI , person is considered to have obesity when having BMI ≥30 (4).

- **Changes in Gut Hormones and Obesity:**

a) Orexigenic Hormones:

1. Ghrelin:

Gherlin is a peptide hormone secreted mainly by P/D1 cells (lining the fundus of the stomach) during the preprandial state. It binds to the growth hormone secretagogue receptor (GHSR1a) in the hypothalamus. The main function of gherlin is stimulating hunger and food intake. Plasma ghrelin levels are lower in obese patients. Studies reported that this decrease thought to be compensatory to the positive energy balance, rather than causal of obesity, in these patients (5).

2. Motilin:

Motilin released by the M-cells in the small intestine which stimulates gastrointestinal motility initiating a pattern of strong contractions in the distal stomach or small intestine during the interdigestive phase which clean the intestine of food remnants. Higher plasma motilin levels with fewer fluctuations in the fasting state noticed in obese patients, supporting it as a hunger hormone which stimulates food intake in these patients (5).

b) Anorexigenic Hormones:

1-Cholecystokinin (CCK):

Cholecystokinin secreted mainly by enteroendocrine cells (EEC) in the GIT tract mainly in the duodenum and jejunum known as I-cells. In response to food intake particularly fat and protein, it acts through slowing gastric emptying and inhibiting food intake. Obesity blunts the effect of CCK, which means there is insensitivity of vagal afferent neurons to CCK, which leading to reduced effect of CCK on satiety and the fact which most obese people always complain about feeling hungry (5).

2-Glucagon-like peptide-1(GLP-1):

GLP-1 is a proglucagon-derived hormone secreted by L-cells in the small intestine and colon in response to nutrients, GLP-1 levels increase rapidly upon food intake. GLP-1 is a satiety signal which acts as an incretin, meaning it reduces circulating levels of glucose via stimulating insulin secretion. It also acts by inhibiting glucagon secretion, thus reducing endogenous glucose production, reducing food intake and slowing gastric emptying. Studies reported that in obese patients there was about 20% reduction in GLP-1 response to oral glucose compared with normal weight individuals (6).

3-Oxyntomodulin (OXM):

Oxyntomodulin is a 37-amino acid peptide, secreted in response to food intake. OXM is a potent anorectic hormone; it has the same effect as GLP-1 on satiety but with much lower affinity for the GLP-1 receptor (7).

4-Peptide YY:

PYY is a 36 amino acid peptide secreted by L-cells in the distal gut together with GLP-1, GLP-2 and OXM following a meal. Proteins provide the most potent stimuli for the release of

PYY, cleaved to PYY3-36 by the enzyme DPP4 immediately after secretion. Meal-induced PYY3-36 release has been founded to be lower in obese than in lean individuals (7).

❖ **Adipose tissue hormones:**

1. Leptin:

Leptin is a peptide hormone released from adipose tissue and encoded by the obese (LEP or ob) gene, which takes part in the regulation of body weight by controlling food intake and energy expenditure. The amount of leptin in the blood is directly proportional to the amount of adipose tissue. Leptin exerts its actions by binding to leptin receptors on the surface of cells which are present on neuronal, hepatic, pancreatic, cardiac, and perivascular intestinal tissue. Hyperleptinemia is associated with leptin resistance, as a compensatory mechanism to organ-specific leptin-resistant state. Hyperleptinemia and leptin resistance are common components of obesity (8)**.**

2. Apelin:

Apelin has a crucial role in the pathogenesis of insulin resistance as well as T2DM. It is secreted from white adipose tissue and is associated with various functions, including food intake and insulin sensitivity. The level of apelin in obese patients with T2DMis significantly increased compared to healthy people. In obesity and diabetes, insulin could control apelin. During a hyperinsulinemic-euglycemic clamp in nondiabetic human volunteers, apelin perfusion markedly improved insulin sensitivity without causing side effects (9).

Role of Gut Microbiota in pathogenesis of Obesity

The gut microbiota refers to a complicated ecosystem colonized in the human gut tract, which embodies large amounts of microorganisms, including bacteria, fungi, virus, archaea, protists and so on. The total weight of the gut microbiota is about 1-2 kg, and the number of genes it contains is more than 100 times than which of the human body in which it resides. In a healthy status, the gut microbiota coexists harmoniously with the host and participates in the regulation of multiple physiological functions of the host (10).

If an imbalance in bacterial composition, changes in bacterial metabolic activities, or changes in bacterial distribution within the gut happens, it is defined as "Dysbiosis". The altered gut microbiota participates in the pathogenesis of obesity via multiple mechanisms, including energy homeostasis disruption, lipid synthesis and storage, central appetite and feeding behavior dysregulation, as well as chronic low-grade inflammation (11).

Obesity is associated with specific microbial phyla composition; studies reported that the composition and biodiversity of gut bacteria in obese groups significantly differed from those in healthy groups. The analysis of fecal bacteria of obese individuals and lean individuals showed that at the phylum level, the abundance of Firmicutes and the ratio of Firmicutes/Bacteroidetes have increased significantly in obese subjects and the abundance of Bacteroidetes has decreased significantly in such groups compared to lean subjects (11).

Gut dysbiosis in obesity contributes greatly to lipid storage. The altered gut microbiota in obese subjects brings about higher lipopolysaccharide concentration, which triggers a series of inflammation responses and induces metabolic endotoxemia. Leading to increase in the expression of proinflammatory cytokines in adipose tissues (including Interleukin-6 and TNF-α) which can result in insulin resistance. Besides, the gut microbiota is also favorable for lipid storage via the induction of leptin resistance and the inhibition of fat-suppressing neuropeptides (11).

Insulin resistance

Insulin is a peptide hormone produced and released from beta cells of the pancreas (β-cells). Under normal physiological conditions, increased plasma glucose levels lead to increased insulin secretion and circulating insulin levels, thereby stimulating glucose transfer into peripheral tissues and inhibiting hepatic gluconeogenesis. Individuals with defected insulin-stimulated glucose uptake into muscle and adipocytes tissues, in addition to impaired insulin suppression of hepatic glucose output, are described as having "insulin resistance" (12).

There are three broad categories of IR or insulin-deficient conditions: (a) diminished insulin secretion by β-cells; (b) insulin antagonists in the plasma, due either to counter-regulatory hormones or non-hormonal bodies which impair insulin receptors or signaling; and (c) impaired insulin response in target tissues (11).

There are three main extra-pancreatic insulin-sensitive organs which play major roles in these processes, which are skeletal muscle, adipose tissue and liver, a defective action of insulin in these tissues often precedes the development of systemic IR, thus progressively leading T2DM (12).

a) Skeletal Muscle:

Skeletal muscle IR considered the most important extra-pancreatic factor in the development of T2DM. Under physiological conditions, insulin stimulates muscle glycogen synthesis by enhancing glucose uptake from plasma. There are three primary rate-limiting factors implicated in glucose uptake and glycogen synthesis: glycogen synthase, hexokinase and the Glucose transporter type 4 (GLUT4). Upon insulin binding to insulin receptor (INSR) in muscle cells, GLUT4 translocates from intracellular compartments to the plasma membrane. This process allows glucose uptake and reduces circulating glucose levels (13).

Mutations which reduce the expression of insulin receptor or GLUT4, as well as any defect in either upstream or downstream signaling pathway would reduce glucose intake into the muscle resulting in a hyperglycaemic state (4).

b) Adipose Tissue:

Adipose tissue is a metabolically dynamic tissue capable of synthesizing a wide range of biologically active compounds which regulate metabolic homeostasis at a systemic level. Insulin acts on adipose tissue in two different ways: (1) stimulating glucose uptake and triglyceride synthesis; and (2) suppressing triglyceride hydrolysis and inducing the uptake of free fatty acids (FFA) and glycerol from circulation (12).

An impaired response to insulin stimulation by adipose tissue is known as "adipose IR", which is associated with glucose intolerance and elevated release of FFA into plasma which accumulates in other tissues such as muscle or liver (14).

c) Liver:

In the liver, insulin does not only regulate glucose production and utilization but also affects lipid metabolism more broadly. Under physiological states, the combined action of glucagon and insulin allows the precise regulation of hepatic glucose output. While glucagon induces hepatic glucose production, insulin acts as a potent inhibitor of glucose production when its concentration in the blood is elevated (3).

Relation between Obesity, Insulin resistance and T2DM

The association between obesity and insulin resistance is well established, as which most patients with T2DM are overweight or obese and there is a fact which 70% to 80% of patients with T2DM are obese (5).

The term “diabesity” which made by Dr. Ethan Sims referring to the strong relationship between T2DM and obesity in a single word (15). Elevated plasma insulin in people with obesity is an adaptive response, caused by both increased insulin secretion and decreased insulin clearance, to compensate for impaired insulin sensitivity. However, it has also been proposed which increased β-cell insulin secretion in people with obesity may be a primary abnormality which precedes, and contributes to, the development of insulin resistance (16)**.**

If the insulin-resistant condition stays steady over months and years, the β-cells continuously produce more insulin to compensate for the glucose overload. Because of which, β-cells worn out, causing increased blood glucose level. Hyperglycemia, reduced insulin sensitivity, and increased insulin secretion observed 13 years before T2DM is fully diagnosed (13).

Obesity escalates the pathogenesis of T2DM and insulin resistance through the following mechanisms**:**

1. **Obesity and low grade inflammation :**

Elevated levels of pro-inflammatory cytokines or an increased number of white blood cells in the blood or tissue described as "inflammation". Obesity might cause chronic and low-grade inflammation which is involved in the pathogenesis of T2DM. In addition, adipose-specific cytokines (leptin and adiponectin) and inflammatory cytokines (TNF-α and IL-6) are secreted by visceral adipocytes which are triggers of metabolic inflammation and insulin resistance (17).

2. **Excessive Lipid Deposition and Insulin Resistance:**

The storage capacity of single adipocytes is limited, although they have a highly advanced ability to sequester fat. Following a short-term high-fat diet, enlarged adipocytes trigger insulin resistance in the absence of much macrophage infiltration into adipose tissue. Hence, excess lipid in adipose cells results in insulin resistance even without inflammatory responses. This might be justified as, excessive and ectopic lipid accumulation in adipocytes, liver, muscle, and outside may cause insulin resistance through formation of metabolically toxic product (6).

In addition, the level of hepatic diacylglycerol shows a strong association with systemic insulin resistance, especially in nonalcoholic fatty liver disease. These lipids may activate signaling pathways which negatively affect insulin signal transduction. Incomplete FA

oxidation products may also affect the steps in the insulin signaling cascade or the pathways it controls (17) .

3. Role of adipocytes as an endocrine cells:

The essential role of adipocytes is energy storage and triglycerides synthesis. They also act as endocrine cells; thereby secrete many peptide hormones and cytokines such as TNF-α, plasminogen-activator inhibitor-1, which involves maintaining the level of angiotensinogen and its proteolytic product, which controls vasoconstriction. In addition, adipose tissue produces leptin, aplin and active steroid hormones including estrogen and cortisol. Over such produced molecules, adipocytes retain the capacity to perform their local functions and systemic metabolism in different organs like muscle, brain, liver and blood vessels (12).

4. **Adipokines and Insulin Resistance:**

Patients with T2DM and insulin resistance often exhibit signs of impaired metabolism, deposition, and concentration of lipids in the skeletal muscle and blood. An abundance of free FAs in the plasma reduces insulin-regulated glucose metabolism. Various adipokines (such as adiponectin, TNF-α, resistin, and IL) are involved in this disease state. An increase in the level of adiponectin enhances insulin sensitivity while resistin exhibits insulin-antagonistic effects (8)**.**

Conclusion

Given these connections, most treatments available for obesity and T2DM have a mutual effect on each other. Future efforts are warranted in the work and multi-disciplinary collaborations in monitoring the prevalence and revealing the biological nature of obesity and T2DM to improve the accuracy of the diagnosis and the efficacy of the treatments. It is noteworthy that prevention is still the most economic and long-lasting solution for obesity and T2DM, and only by striving together and taking decisive and comprehensive action can the whole world make real progress in this task that we have been failing for decades.

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