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Metabolic risk factors in obesity and diabetes mellitus: implications in the pathogenesis and therapy

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Abstract

The increased prevalence of obesity worldwide is a serious problem as it invites several other metabolic chronic disorders including Diabetes mellitus, one of the major global pandemic now a days. Obesity raises the propensity of developing insulin resistance and type 2 diabetes mellitus (T2DM) by several folds. Adipose tissue derived increased amounts of non-esterified fatty acids, glycerol, hormones, proinflammatory cytokines and other factors are involved in the development of insulin resistance in obese individuals. When insulin resistance is accompanied by pancreatic islet β-cell dysfunction, glycemic control worsens resulting in diabetes. Abnormalities in β-cell function are therefore critical in defining the risk and development of type 2 diabetes. Although clinical studies aimed at reducing the deleterious effects of these conditions have been conducted or are undergoing trials, detailed exploration of the molecular and metabolic basis of the disease may guide us to new approaches to its prevention and treatment.

Introduction

Obesity is a complex trait caused by an excessive accumulation of adipose tissue and influenced by diet, developmental stage, age, physical activity and genetic makeup [1]. It is considered as a health disaster and the prevalence is increasing significantly in both developed and developing countries [2]. It results from an imbalance between food intake and energy expenditure causing an excessive accumulation of adipose tissue [3]. The prevalence of obesity worldwide is estimated to 500 million adults of which 1.5 million people are overweight or obese [4]. The body mass index (BMI) is used to define obesity, which will be defined as a BMI 30 kg/m^2 or greater as stated [5]. The most devastating outcome of obesity istype 2 diabetes mellitus (T2DM) as its prevalence is expected to increase from 171 million people at the start of this century to 360 million people by 2030 [5]. Insulin resistance is the common link associated with obesity and diabetes mellitus. It is due to decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose production. Pathologically various mechanisms contribute to the development of insulin resistance such as impaired insulin and insulin receptor interaction in the periphery, alteration in insulin signaling molecules like IRS 1 and 2, Protein kinase B (Akt), C, decreased expression of insulin receptors or translocation of glucose transporters (GLUT) [6].

Diabetes mellitus (DM) is a metabolic syndrome which alters carbohydrate, protein, fat and energy metabolism and is caused by the absence of insulin secretion or due to defects in insulin action in the peripheral tissue [7]. Inappropriate insulin production from pancreatic β-cells and peripheral insulin resistance are the two key factors T2DM pathogenesis[8]. Insulin resistance may result in elevated fatty acids in the plasma, decreased glucose transport into the muscle cells, and increased fat breakdown, which leads to higher hepatic glucose production. Despite insulin resistance being the common link between obesity and T2DM,all the obese subjects do not develop hyperglycemia due to insulin resistance as beta cells of Langerhans release appropriate amounts of insulin to maintain normal glucose tolerance. Moreover, endothelial dysfunction and nonesterified fatty acids (NEFAs) are also linked with obesity or insulin resistance in T2DM [9-11]. Studies in dogs suggest that it is the nocturnal elevations in NEFAs that might underlie the β-cell's adaptive response to insulin resistance[12]. Elevated NEFA levels produced by a lipid infusion *in vivo* contribute to the development of insulin resistance and also prevent the expected compensatory β-cell response in humans[13]. This dual effect makes them a good candidate to link insulin resistance and β-cell dysfunction in individuals with type 2 diabetes and those at risk of the disorder. This lipotoxic effect can also act synergistically with glucose to produce even greater deleterious effects, commonly referred to as 'glucolipotoxicity'.

This review attempts to explore the metabolic risk factors associated with obesity and T2DM and their preventive management therapies.

Risk factors in obesity and T2DM

There are multiple risk factors associated with obesity and diabetes mellitus which includes physical inactivity, sedentary lifestyle, family history, high risk ethnicity, cardiovascular disease (CVD), dyslipidemia, hypertension, sleep apnoea, renal disease, and others[14]. The gene polymorphisms in ADIPOQ (rs1501299 and rs17300539), LepR (rs1137101 and rs1045895), IRS2 (rs1805092), GRB14 (rs10195252 and rs3923113) and PPARG (rs1801282) have also been associated with overweight and obesity in uncontrolled T2DM [15]. Apart from the gene polymorphisms, population based long-term prospective and cross-sectional studies have identified many risk factors of T2DM as well as obesity, and some of these like altered blood levels of adipokines, chemokines, elevated circulating proinflammatory cytokines, vitamin

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D deficiency and dyslipidemia have obvious metabolic connotation. Neural signalling might also regulate β-cell mass. Experimental VMH lesion mediated model of obesity and insulin resistance has beenfound to be associated with vagal hyperactivity and proliferation of islet cells, particularly β-cells [16]. Thus, it is plausible that increased vagal input associated with diet-induced obesity might also contribute to extensive innervation with increased β-cell mass and alteration in the insulin sensitivity.

Chemokines

Chemokines play a major role and their receptors are expressed in visceral and subcutaneous adipose tissue in obesity [17]. C-C motif chemokine ligand 2/macrophage chemoattractant protein-1 (CCL2/MCP-1) is the key chemokinewhich is involved in migration and infiltration of macrophages, initiates inflammation by attracting inflammatory cells from the blood stream into adipose tissue [18,19]. One of the studies observed that circulating CCL2/MCP-1 was higher in type 2 diabetes subjects and presence of the *MCP-1* G-2518 allele was associated with lesser CCL2/MCP-1 levels as well as occurrence of insulin resistance and type 2 diabetes [20]. Moreover, another study showed that *MCP-1* G-2518 gene variant decreased the risk of type 2 diabetes [21,22]. Apart from CCL2/MCP-1, several other chemokines such as CCL5, C-X-C motif chemokine ligand 5 (CXCL5) and CXCL14 were also involved in adipose tissue macrophage infiltration and obesity-induced insulin resistance [23-25].

Proinflammatory cytokines

Proinflammatory cytokines such as TNF-α, IL 6, IL 18 also add to the pathogenesis of obesity and insulin resistance [26,27]. Adipose tissue contributes to 10-35% of circulating IL-6 levels in humans [28]. Expression of IL 6 and TNF-α are positively correlated with insulin resistance both *in vivo* and *in vitro* [26,29]. Hyperglycemia results in increased IL-6 or TNF-α levels and treatment with IL-6 or TNF-α induces hyperglycemia and insulin resistance in humans [26,30,31]. *IL-6* deficit has also been shown to cause obesity and insulin resistance in mice [32]. Insulin resistance is not induced by TNF-α when *IL-6* is down-regulated in adipose tissue [33]. Moreover, circulating IL-18 levels have been observed to be increased in obese subjects and reduced with weight loss and its overexpression enhanced insulin resistance in a rat model of metabolic syndrome [34,35].

Adipokines

Leptin is a 16 kDa polypeptide product of obese (ob) gene and is synthesized and secreted from the white adipose tissue of our body. It is involved in the regulation of glucose homeostasis, energy homeostasis and also has an important role in body weight regulation [36]. Leptin resistance occurs primarily due to increased circulating leptin levels and its mRNA expression in adipose tissue in obese subjects [37,38]. Leptin regulates pancreatic β-cell function as well as improves insulin sensitivity in the liver and skeletal muscle [39]. Leptin alongwith monocytes induces the release of pro-inflammatory cytokines such as TNF-a or IL-6 as well as CCL2 and VEGF[40]. Leptin helps to maintain a chronic inflammatory state in obesity as its synthesis and release is regulated by the pro-inflammatory cytokines [41].

Adiponectin is another adipocytokine that produces insulin-sensitizing effects,enhances glucose uptake in the liver and skeletal muscles and increases fatty acid oxidation [42,43]. The adiponectin inhibits T cell activation and proliferation in an immune system via the NFκB pathway [44]. Adiponectin oligomers acts via *adiponectin receptor AdipoR1* and*AdipoR2* which are reduced in insulin resistance and mediate the anti-metabolic actions [45].The circulating adiponectin levels are lower in obese as well as in diabetic individuals, and treatment with adiponectin increases insulin sensitivity in animal models [46-48]. The concentrations of inflammatory mediators like TNF-a or IL-6 increases in obesity which leads to decrease in adiponectin expression and release [44].Adiponectin deficiency induces insulin resistance whereas adiponectin over-expression improves insulin sensitivity and glucose tolerance in mice [49].

Resistin is considered a pro-inflammatory adipokine which activates NFkB-dependent cytokine release including TNF-a or IL-6 also plays a vital role in the pathogenesis of diabetes and its complications.Its role in obesity and insulin resistance in humans is controversial [50].

Obesity and dyslipidemia

Obesity and diabetes are linked to an increased prevalence of dyslipidemia. An increased level of plasma free fatty acids, cholesterol and triglycerides, decreased levels of high-density lipoprotein (HDL), and altered low-density lipoprotein (LDL) is seen and are associated with a higher risk of cardiovascular disease.

The metabolic effects of subcutaneous and intra-abdominal fat differ which may be due to differences in adipose tissue distribution. Furthermore, abdominal fat which isconsidered to be more lipolytic than subcutaneous fat, also does not respond easily to the antilipolytic action of insulin, which makes intra-abdominal fat more important in causing insulin resistance, and thus leads to diabetes mellitus. The body fatty acid release is higher in obese subjects as compared to lean subjects because of their greater fat mass [51]. One of the study found the association between enlargement of visceral adipocytes and dyslipidemia independent of body composition and fat distribution in obese subjects [52]. A similar association was also seen in patients with type 2 diabetes [53]. Many adipose-produced inflammatory molecules, including TNF-α, IL-6, IL-1, serum amyloid A (SAA) and adiponectin, and the number of adipose macrophages, due to macrophage infiltration in adipose tissue also play an important role in the development of dyslipidemia.

Vitamin D

The roles of vitamin D beyond calcium homoeostasis and bone metabolism have emerged linking the fat-soluble vitamin to obesity and T2DM [54]. It appears to enhance insulin sensitivity through different mechanisms [55]. Further, vitamin D deficiency has been shown to activate inflammation, cytokine release, upregulation of nuclear factor κB and tumor necrosis factor α, and to raise serum levels of parathyroid hormone [47,56]. Recent studies have found a strong link between vitamin D deficiency, obesity and metabolic syndrome [57]. Furthermore, various prospective epidemiological as well as cross sectional studies have shown that low serum 25(OH) D concentrations are associated with T2DM[47,58,59]. A number of hypotheses have been proposed to explain the possible mechanisms whereby alterations in the vitamin D endocrine system occur in the obese state. The plausible mechanisms include sequestration in adipose tissue, volumetric dilution or negative feedback mechanisms from increased circulating 1,25-dihydroxyvitamin D_3.These patients also commonly consume vitamin-poor diets, which may also contribute to the low vitamin D levels observed.

Prevention and therapy

The preventive measure is the prime key for the management of T2DM and obesity. The key includes diabetes and obesity education,

physical exercise and weight management, nutrition, medication adherence, stress and lifestyle management, and blood pressure regulation [60]. Planfully promoting exercise in obese individuals as well as in diabetics has got multiple benefits: increased insulin sensitivity in tissues, boosting metabolism, improvement of glycaemic control, balancing lipid profile, cardiovascular health, relieving psychological stress and better quality of life [61]. The successful management of the disease depend on the patient's decision and their willpower to control their lifestyle, though health care provider recommendation is of good value [62]. There were two recent studies done for treating prediabetes and diabetes through weight loss, using physical activity and calorie restriction namely Diabetes Preventive Program and Look AHEAD trial [63]. The clinical outcome of the study was intentional weight loss of at least 7% which improved several risk factors associated with the pathogenesis of the disease. It is however worth to mention that the degree and duration of exercise should be carefully prescribed to the patients keeping in mind the diabetic or overweight related complications eg, neuropathy, arthritis etc. Specially weight bearing exercises affecting the lower extremities and joints should be avoided in the initial phase. However, activities like moderate walking, aerobic exercises are good enough to start with. While recommending exercise,doses of hypoglycemic drugs or insulin should be adjusted before and after exercise in order to prevent the appearance of hypoglycemia that can happen due to increased glucose needs.

The caloric intake in the elderly should be between 25 and 35 kcal/kg per day [64]. Protein should provide 15%-20% of total calories, fat 30% maximum, avoiding saturated fats and trans fats, and promoting the consumption of monounsaturated fats and omega 3 fatty acids, and carbohydrates 50-55% based on complex carbohydrates. A dietary fiber intake of about 14 g/1000 kcal is recommended, and they may also require calcium and vitamin D and vitamin B12 supplements.

Future directions

Diabetes and obesity, two chronic metabolic disorders, are alarmingly rising in the modern-day world bringing along with them hundreds and thousands of complications and morbidity. Body mass index has a strong relationship to diabetes and insulin resistance. In an obese individual, the amount of NEFA, glycerol, hormones, cytokines, proinflammatory substances, and other substances that are involved in the development of insulin resistance are increased. Insulin resistance with impairment of β-cell function leads to the development of diabetes. Gaining weight in early life is associated with the development of type 1 diabetes.Given the high prevalence of obesity in children, new approaches in managing and preventing diabetes in obese individuals must be studied and investigated based on these facts. Secondary prevention seeks to prevent further weight gain in individuals who are already overweight or obese. The goal of tertiary prevention is to prevent complications due to co-occurring health problems (e.g., type 2 diabetes) in individuals who are already obese and diabetic.

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