

# Obesity and diabetes: interrelationship

## Abstract

Diabetes epidemic can be attributed to the increasing incidence of obesity, especially in India. It is estimated that about 60-90% of all the patients with type 2 diabetes are obese ( $BMI \geq 30 \text{ kg/m}^2$ ) or overweight ( $BMI \geq 25 \text{ kg/m}^2$ ). A number of mechanisms involved in the pathogenesis of obesity have been proposed which play an important role in the development of diabetes by causing insulin resistance or hypersecretion of insulin. Excessive storage of fat in obese people leads to the release of excessive fatty acids resulting in insulin resistance and hyperglycemia. Insulin resistance is also a consequence of elevated secretion of cytokines (TNF- $\alpha$ , IL-6, complement C3, MIF and leptin) by the adipose tissue resulting in the development of diabetes. There is a close association of diabetes and obesity with low plasma concentrations of adiponectin however, further experimental studies are required to establish the role of adiponectin. Development of both the diseases can be prevented to a large extent by increasing physical activities and maintaining a healthy weight. We undertook this review to study the interrelationship between diabetes and obesity.

**Keywords:** obesity, type 2 diabetes, adipokines, cytokines

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Samreen Siddiqui

Independent researcher, India

**Correspondence:** Samreen Siddiqui, Independent researcher, M-301 Taj Enclave, Geeta Colony, Link Road, Delhi-110031, India, Tel 9582865898, Email sid.samreen@gmail.com

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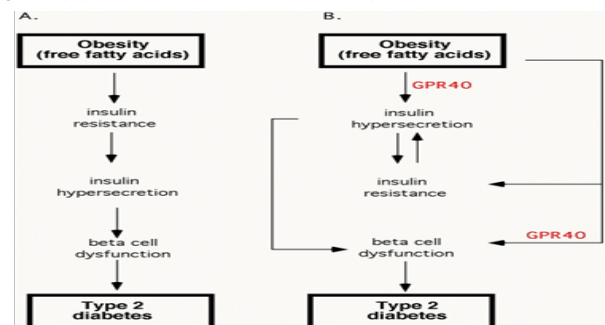
## Introduction

Diabetes is one of the major health problems affecting large number of individuals and has reached epidemic proportion worldwide. The World Health Organization (WHO) has projected that around 300 million people will suffer from diabetes by 2025.<sup>1</sup> Among the well-known risk factors of diabetes one of the most important and major risk factor is obesity ( $BMI \geq 30 \text{ kg/m}^2$ ),<sup>2</sup> whose prevalence is also rising at a higher rate in developing countries, including India.<sup>3,4</sup> Around 60-90% of all patients with type 2 diabetes are obese.<sup>5,6</sup> The increasing incidence of diabetes can thus be attributed to the global epidemic of obesity.<sup>7</sup> A number of clinical studies have reported an association between obesity and insulin resistance in adults as well as children<sup>8-10</sup> and reports are also present which suggest that weight loss is associated with a decrease in insulin concentration and an increase in insulin sensitivity in adults and adolescents.<sup>11,12</sup> This comorbid condition of obesity in patients with type 2 diabetes is very common and is often termed as “Diabesity”.<sup>13,14</sup> Sedentary lifestyle and changing food habits could be the main reasons for continuously increasing incidence of obesity and diabetes both in the urban as well as the rural areas in India. The rising prevalence of these two diseases is of concern as they may act as major risk factors for other fatal conditions like coronary artery disease (CAD). The aim of this review article was to study the relationship between obesity and diabetes. This is a general review and we reviewed fifty research papers before writing this paper.

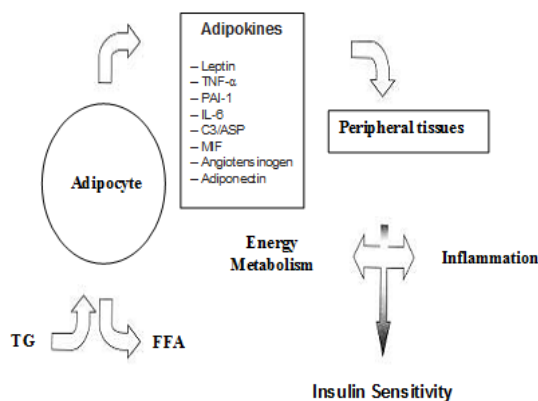
## Pathophysiology of obesity and type 2 diabetes

Pathogenesis of obesity appears to play a central role in the dysregulation of cellular mechanism that accounts for insulin resistance, which is the state of reduced responsiveness of liver, muscle and adipose tissue to insulin in type 2 diabetes. The stored fat is required for survival during nutritionally deprived states, however during state of prolonged abundance of food, excessive fat storage results in obesity.<sup>15,16</sup> This excessive storage of fat that creates obesity

eventually leads to the release of elevated levels of fatty acids (FFAs) from enhanced lipolysis. The release of these FFAs then induces lipotoxicity, as lipids and their metabolites create oxidant stress to the endoplasmic reticulum and mitochondria. This affects adipose as well as non-adipose tissues resulting in insulin-receptor dysfunction. The consequence is an insulin-resistant state which then creates hyperglycemia with compensated hepatic gluconeogenesis.<sup>17-19</sup> Insulin resistance is a key factor for type 2 diabetes. FFAs also decrease utilization of insulin-stimulated muscle glucose, contributing further to hyperglycemia. Lipotoxicity from excessive FFAs also decreases secretion of pancreatic  $\beta$ -cell insulin, which eventually results in  $\beta$ -cell exhaustion (Figure 1). Moreover, excess adipocytes release inflammatory adipokines (TNF- $\alpha$ , IL-6, complement C3, leptin and MIF), which, along with free fatty acids, provide the pathophysiologic basis for comorbid conditions associated with obesity such as insulin resistance and type 2 diabetes. Along with fatty-acid lipotoxicity, visceral adipokines also contribute to the adipokine inflammatory injury that leads to pancreatic  $\beta$ -cell dysfunction, which, in turn, decreases insulin synthesis and secretion.<sup>20,21</sup> Adipocytes also stimulate fat-associated macrophages that also secrete monocyte chemoattractant protein 1 (MCP-1), macrophage migration inhibiting factor (MMIF), and resistin, all of which decrease insulin sensitivity (Figure 2) (i.e. enhance insulin resistance).<sup>22,23</sup>



**Figure 1** Pathway showing development of diabetes due to obesity.



**Figure 2** Adipokines regulating insulin sensitivity

## Obesity and diabetes interlinked

A strong relationship between obesity and the onset of diabetes has been reported in a number of studies. Research has shown that people carrying more weight particularly around the tummy are more insulin<sup>24–27</sup> resistant and may struggle to achieve good diabetes control.<sup>10,28,29</sup> A number of mechanisms have been proposed to link obesity and insulin resistance which predispose to diabetes and includes increased production of adipokines or cytokines including tumor necrosis factor- $\alpha$ , resistin and retinol-binding protein 4.<sup>30</sup> Excess body fat and particularly visceral fat release increased amounts of FFAs in the blood. Elevation of FFAs levels directly affects insulin signaling and causes the liver and skeletal muscles to shift towards greater oxidation of FFAs for energy production and a relative inhibition of enzymes in the glycolytic cascades. As a result the capacity of liver and skeletal muscles cells to absorb and metabolize glucose decreases. Also, the tissues capacity to store glucose as glycogen decreases and the cells accumulate more triglycerides instead of glycogen.

Further, in an Indian the body fat percentage is significantly higher than a western counterpart with similar BMI and blood glucose level. It has been hypothesized that excess body fat and low muscle mass may explain the high prevalence of hyperinsulinemia and the high risk of type-2 diabetes in Asian Indians.<sup>31</sup> The risk of diabetes increases exponentially as BMI increases above about 25 kg/m<sup>2</sup>.<sup>32,33</sup> In a large cross-sectional study in middle aged Indians, a BMI>23 was found to be associated with increased risk for type 2 diabetes.<sup>34</sup> Visceral fat increases the risk of diabetes by favouring insulin resistance. Patients with diabetes are usually advised to increase their physical activity and reduce weight. Prolonged duration of obesity also have deleterious effects on glucose homeostasis like increased resistance to glucose disposal and decreased secretion of insulin. Resistance to glucose disposal is strongly associated with obesity and results in high fasting and postload serum insulin concentrations. Prolonged duration of obesity could conceivably worsen this resistance.<sup>35</sup> Although excess fat in any region of the body is associated with increased risk of type 2 diabetes, it is generally held that an accumulation of abdominal fat ('central' obesity), as indicated by an increased waist: hip ratio is an independent risk for type 2 diabetes irrespective of the extent of obesity.<sup>36,37</sup> This is mainly attributed to increased intra-abdominal

(visceral) adiposity. Excessive deposition of lipid in muscle and liver also enhances the risk of type 2 diabetes through mechanisms of intracellular lipotoxicity.

## Genetic factors linking obesity and diabetes

Obesity as well as diabetes, both are the examples of multifactorial diseases that arise through the interaction of multiple genetic and environmental factors. There has been evidences present which establish the genetic link between obesity and diabetes. Genome-wide association scans (GWAS) and candidate gene approaches have identified 40 genes associated with type 2 diabetes and a similar number, although largely different, with obesity. Most type 2 diabetes genes appear to be related to b-cell dysfunction, with many fewer involved in pathways related to insulin resistance independent of obesity.<sup>38–41</sup> A growing understanding of genetics and cellular function of the b-cell can identify potential mediators predisposing obese individuals to type 2 diabetes and further may provide insights for the development of new therapeutic agents. Although numerous diabetes and obesity associated genes have been identified, the known genes are estimated to predict only 15% of type 2 diabetes and 5% of obesity risk.<sup>42,43</sup> Recent genome-wide studies have shown multiple loci on chromosomes which affect the obesity-related phenotypes.<sup>44</sup> It can be speculated that the susceptibility to type 2 diabetes and obesity might also partly be due to shared genes. By comparing all of the published genome scans for type 2 diabetes and obesity, five overlapping chromosomal regions for both diseases have been identified and by analysing these five susceptibility loci for type 2 diabetes and obesity, 27 functional candidate genes have been pinpointed that are involved in eating behaviour, metabolism and inflammation. These genes might reveal a molecular link between the two disorders.<sup>45</sup> By comparing the defined obesity-relevant pathways and Non-insulin dependent diabetes mellitus (NIDDM)-relevant pathways, it has been found that obesity-relevant pathways contains a gene set related to the insulin receptor, and coincidentally, there is a NIDDM-relevant gene set containing genes 2-fold up-regulated by insulin. Other than that, all relevant pathways in obesity and NIDDM are literally different.<sup>46</sup>

## Co-relation of adiponectin, obesity and diabetes

Adiponectin is a novel fat protein secreted by adipose tissue and abundantly present in the circulation in humans. It has been hypothesized that this protein has a role in the pathogenesis of obesity and type 2 diabetes and that lower plasma levels of adiponectin are predictive of type 2 diabetes and found in patients with diabetes as well as in obese people.<sup>29,47–49</sup> A review done by Hussain et al.,<sup>50</sup> has reported that concentrations of adiponectin may be down regulated by weight gain. Diabetes and obesity both are associated with low plasma adiponectin concentrations and hypoadiponectinemia in obese people is in large part attributable to insulin resistance.<sup>51</sup> A previous study in Japanese individuals have shown that the plasma adiponectin concentration is negatively correlated with body mass index (BMI) and therefore found to be lower in obese than in lean subjects,<sup>52</sup> which is also the case in Indian population.<sup>53</sup> However, the mechanism behind this close association between plasma concentration of adiponectin and insulin sensitivity is still unknown. Further experimental studies are required to study the molecular link between plasma levels of adiponectin and the pathogenesis of obesity and diabetes.

## Conclusion

Obesity and diabetes which have become major health problems in India as well as globally are closely linked together, obesity serves as a major risk factor for type 2 diabetes and weight gain management can reduce the risk of diabetes to a larger extent. Urbanization, changing life style & food habits are the main reasons for increasing obesity in India and consequently responsible for increasing incidence of diabetes. Increasing physical exercise and maintaining ideal weight can lower the chances of developing diabetes. Further, reducing FFAs levels should be an important goal in the management of patients with type 2 diabetes mellitus. Preventing obesity (BMI $\geq$ 30kg/m<sup>2</sup>) could largely prevent diabetes. More large-scale clinical studies are required to understand the molecular mechanisms behind obesity causing insulin-resistance and the genetic relationship between both the diseases in order to develop better therapeutic remedies.

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## Conflict of interest

The authors declare there is no conflict of interest.

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