Targeting Obesity for the Treatment of Type 2 Diabetes Mellitus
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Abstract
The discovery of diabetes mellitus (simplified as “diabetes”) could be traced back to 1500 B.C. The first detailed description appeared in 1800, but in the last few decades, the prevalence of diabetes increases dramatically. Till present, according to WHO’s report, 247 million people worldwide have been diagnosed Diabetes, among which 3.47 million died from diabetes. Thus, WHO projects that diabetes will become the 7th leading cause of death in 2030. The typical feature of diabetes is hyperglycemia as a result of metabolic disorder. As the disease progress, complications develop including macrovascular and microvascular abnormality, leading to multiple organ failure and mortality. Apart from diabetes-associated vascular diseases, numerous studies have documented the association between hyperglycemia and cancer. There are three main types of diabetes: (1) type 1 diabetes mellitus (T1DM) in which pancreatic β cell death by immune attack; (2) type 2 diabetes mellitus (T2DM) in which pancreatic β cells fail to produce sufficient amount of insulin; and (3) gestational diabetes which occurs in pregnant women due to high demand for insulin production. Type 2 DM accounts for 80–90% of diabetes and obesity has been identified as a strong and modifiable risk factor in type 2 DM. In this review, we first provide a general introduction of T2DM in the aspects of diagnosis, pathogenesis and clinical characteristics of T2DM. We will focus on how obesity has the adverse impact on insulin resistance, pancreatic β cell death and dysfunction and the development of T2DM. Next, we will summarize the animal models of T2DM including their advantages and drawbacks when compared to their clinical relevance. Finally, we will summarize the interventions that have been applied to treat obesity and T2DM and the remaining problems.

Keywords: Obesity; Diabetes; Pancreatic β cells; Hepatocytes, Gastric bypass

General Introduction of T2DM
Definition and diagnosis criteria of T2DM
Hyperglycemia is the main feature of diabetes, thus, plasma glucose level remains the solo and golden standard in the diagnosis of the disease. According to WHO’s recent recommendations, the threshold of glucose level for diagnosis of diabetes, impaired glycemic tolerance (IGT) and impaired fasting glucose (IFG) are summarized in Table 1. One whose fasting glucose level exceeds 7 mmol/l or 2-h oral glucose tolerance test (OGTT) exceeds 11.1 mmol/l is diagnosed as diabetes. Different from that, diagnosis of IGT and IFG require both criteria.

Pathogenesis of T2DM
In addition to diet and life style, both environment and genetic factors contribute to the manifestation of T2DM. Up to date, more than 36 genes have been identified to contribute to T2DM, most of which are involved in pancreatic β cell function [1]. As a result of diet and life style changes, obesity develops and becomes a strong independent risk factor in T2DM. Despite the etiological factors are diverse and varied, the underlying pathogenesis of T2DM remains the same: insulin resistance, β cell hyperplasia and insulin insufficiency. Physically, plasma level of glucose increases after diet, which stimulates pancreatic beta cell to secrete insulin. Insulin, on one hand promotes glucose uptake and metabolism in the liver, skeletal muscle and fat tissues, on the other hand, enhances glycogen synthesis, leading to glucose homeostasis. In pathological conditions such as obesity, excess body fat, particularly visceral fat, releases large amount of free fatty acid into blood. The free fatty acid interferes with insulin signaling by (1) being absorbed by liver and skeletal muscle and thus becomes the main fuel for energy production; and (2) increased triglyceride storage in liver and skeletal and inhibition of glycogen synthesis. This reduced effect of liver and skeletal in responses to insulin is so called “insulin resistance”.

To overcome sustained high level of glucose in blood, pancreatic β cells have to produce more insulin. The compensation response consists of both insulin production and increased β cell number so

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>Impaired glucose tolerance (IGT)</th>
<th>Impaired fasting glucose (IFG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>&lt;7 mmol/l</td>
<td>6.1-6.9 mmol/l</td>
</tr>
<tr>
<td>Plasma</td>
<td>(126 mg/dl)</td>
<td>(110-125 mg/dl)</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-h OGTT*</td>
<td>11.1 mmol/l</td>
<td>&lt;7.8 mmol/l</td>
</tr>
<tr>
<td>(200 mg/dl)</td>
<td>(140-200 mg/dl)</td>
<td>(140 mg/dl)</td>
</tr>
</tbody>
</table>

*2-h OGTT: plasma glucose level at 2 hours after oral ingestion of 75 g glucose

Table 1: Plasma glucose level in the diagnosis of diabetes.

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patients develop retinopathy and the prevalence increases with the progression of diabetes and hypertension [10]. In American, retinopathy-induced blindness is the main cause of blindness than any other cause. Retinopathy is usually graded into background and proliferative retinopathy [11]. Although it is not clear how retinopathy develops, endothelial cell damage, thickening of basement membrane, tiny hemorrhages and microaneurysms are characteristic of background retinopathies. In progress, neovascularization and fibrovascular proliferation may occur in the progression of background retinopathy toward proliferation retinopathy. The new capillaries are more fragile with more leakage. It is only when pathological changes encroach on the macula that visual impairment and blindness occur.

b. Diabetic nephropy: Diabetic nephropy affects about 33% of T2DM patients [12]. The earliest clinical sign of nephropy in T2DM is the detection of small amount of proteins in the urine (termed microalbuminuria). Over decades, larger amount of proteinuria develops, leading to chronic renal failure.

c. Diabetic peripheral neuropathy (DPN): DPN affects approximately 50% of diabetic patients, therefore, it becomes the most prevalent complication of diabetes [13]. Because of pathological change in the nerve, patients lose sensation of temperature but sense chronic pain, more severely recurrent foot ulceration. Amputation may be taken in pain relief and prevention of further ulceration and infections.

Diabetes-associated carcinoma: The diabetes-, obesity-related cancer was noticed in 1934. In these decades, extensive studies have been performed to interpret whether and how cancer occurs in response to diabetes, hyperinsulinemia and hyperglycemia. Table 2 provides an overview of the incidence of cancer in patients with obesity and diabetes. Although the mechanisms are not fully understood yet, the dysregulated insulin-insulin growth factor 1 (IGF-1) pathways and specific hormones have been demonstrated to play major roles in the occurrence of cancer in diabetes patients.

The Impact of Obesity on T2DM

The positive association between obesity and the prevalence of diabetes

As a consequence of lifestyle changes, obesity becomes epidemic worldwide. The definition of overweight and obesity directly comes from body-mass index (BMI) while waist circumference serves as a reference. Definition of normal weight, overweight and obesity is shown in Table 3. To be addressed, the obesity criteria may slightly vary from ethic races. For example, in Asians, BMI 23 kg/m² can be used to define overweight and BMI 25 or 27 kg/m² can be used to indicate obesity. The worldwide prevalence of obesity is summarized in Figure 2. Accumulated evidence has identified that obesity is an independent risk factor in cardiovascular disease, [14-16] diabetes, [16-20] and hypertension [20,21]. Population-based studies consistently point out the intimate association between obesity and diabetes as a function of prevalence (Figure 3).

The molecular mechanisms underlining the adverse effect of obesity on T2DM

From a global view, adipocytes in obese subjects not only disturb glucose metabolism but also illicit inflammation cascade by producing
Type of study | Study size | Overall incidence of cancer or findings | Cancer subtype
--- | --- | --- | ---
Zhang et al. [79] cohort study | 7,950 T2DM subjects | 108.36/10^5 subjects in men; 870.2/10^5 subjects in women | Pancreatic cancer liver cancer; kidney cancer breast cancer
He et al. [80] Meta-analysis | 2,596,856 T2DM Patients | 66.68-84.51 per 100,000 person-years | Bladder cancer
Yang et al. [81] Meta-analysis | 643,683 DM patients; 4,819,656 non-DM patients | Increased risk of cancer in DM patients compared to non-DM patients | Bladder cancer
Adami et al. [82] Cohort study | 153,852 T2DM patients | 819 incident cancers in 1-24 years | Primary liver cancer, biliary tract cancer
Chari et al. [83] Cohort study | 2122 diabetic patients | 1% subjects diagnosed cancer in 3 years | Pancreatic cancer
Redaniel et al. [84] Cohort study | 52,657 T2DM female patients | A 29% overall cancer risk in DM patients; Positive association between diabetes and breast cancer | Breast cancer
Park et al. [85] Retrospective study | 1213 men in which 408 subjects were obese | Positive association between obesity and cancer | Prostate cancer
Larsson et al. [86] Meta-analysis | 11,079 subjects | Obese persons with increased risk of cancer | Liver cancer
Olsen et al. [87] Meta-analysis | 28 studies | Positive association between obesity and cancer | Ovarian cancer
Key et al. [88] Prospective study | 624 obese subjects and 1669 controls | Positive association between obesity and cancer | Breast cancer

Table 2: Association between obesity, diabetes and cancer.

adipokines such as resistin and inflammatory cytokines such as TNF-α, monocyte chemoattractant proteins 1 (MCP-1) and interleukins. In this section, detailed overview is provided to understand the pathological machinery of obesity in T2DM.

**Obesity and the fate of pancreatic β cells:** In obesity, adipocytes produce and release huge amount of free fatty acid (FFA). Prolonged exposure of FFAs to β cells inhibits insulin synthesis [22] and impairs conversion of proinsulin to insulin [23,24]. In parallel, overloading FFAs to β cells promotes ER stress as evidenced by activation of ATF6 and XBP-1 and CHOP up-regulation. Exposure of high glucose and FFAs increases reactive oxygen species (ROS) production and leads to mitochondrial dysfunction in β cells [25,26]. Resistin is specifically expressed and secreted by adipocytes, whose expression is negatively regulated by β cells and by activation of PPAR γ [27,28]. Resistin antagonizes insulin action and reduces glucose uptake in peripheral tissue [28,29]. Apart from its negative effect on metabolism, it increases transcription of several inflammatory cytokines such as IL-1, TNF-α in an NF-κB-mediated fashion [30,31]. Furthermore, it upregulates intercellular chemotactic molecule-1 (ICAM-1), vascular cell-adhesion molecule-1 and CCl12 expression on endothelial cells, leading to enhanced recruitment of leukocytes [32]. Leptin, a hormone secreted from adipocytes, restricts food intake and enhances energy consumption. Moreover, it is involved in the inhibition of insulin synthesis and secretion. The net effect of leptin tends to adapt glucose homeostasis to the amount of body fat. Released by
The pathological process of T2DM in context of obesity, we have to keep in mind that (1) adipocytes are not the only source of cytokine production. For instance, immune cells as well as β cells are reservoirs in cytokine production; (2) the effects of adipokines and cytokines could be different from tissue to tissue, organ to organ and low concentration to high concentration; and (3) the molecular basis of T1DM and T2DM is in large difference. Cytokines-promoted adipocytes, transforming growth factors (TGF-β1) inhibits insulin transcription via TGF-beta/Smad3 axis [33,34]. TGF-β1, together with resistin and inflammatory cytokines TNF-α, plasminogen activator inhibitor-1 (PAI-1) and MCP-1 produced by adipocytes, they stimulate inflammation in both NF-κB dependent and independent manners [26,35-37]. Adipocytes also produce adiponectin that has beneficial effect on insulin release and promote β cell survival [38,39]. Unfortunately, adiponectin secretion is dramatically reduced in obesity [40]. Ultimately, β cells are subjected to dysfunction and death. To be noted, different from these proinflammatory cytokines, IL-6 produced by adipocytes may have dual effects on β cells. Upon engagement of IL-6 to its receptors containing IL-6R and gp130, activation of Janus-associated kinases (JAK) and phospholipase C (PLC)-inositol triphosphate (IP3) pathways has been reported, which is associated with inflammation and enhanced glucose-stimulated insulin secretion, respectively [41-44]. Thus, its function remains controversial. The description of link between adipocytes and β cells is illustrated in Figure 4.

To understand the pathological process of T2DM in context of obesity, we have to keep in mind that (1) adipocytes are not the only source of cytokine production. For instance, immune cells as well as β cells are reservoirs in cytokine production; (2) the effects of adipokines and cytokines could be different from tissue to tissue, organ to organ and low concentration to high concentration; and (3) The molecular basis of T1DM and T2DM is in large difference. Cytokines-promoted NF-κB plays a major role in β cell apoptosis in T1DM. However, FFAs-induced ER stress and β cell apoptosis does not require NF-κB activation.

**Obesity and the fate of hepatocytes:** Glucose homeostasis is tightly controlled by three factors: (1) insulin secreted from pancreatic β cells; (2) glucose uptake by peripheral tissue and liver; and (3) regulation of hepatic glucose output. Therefore, hepatocytes are key players in glucose homeostasis. Before we discussed the adverse effect of obesity on peripheral tissue such as liver, we briefly illustrated the general action of insulin on cells. Following the binding of insulin to insulin receptor that is consisted of 2 α subunits and 2 β subunits, the complex phosphorylates insulin receptor substrates proteins (IRS proteins) at tyrosine residues. The effectors downstream of IRS proteins are phosphoinositide 3-kinase (PI 3-kinase), p42/p44 mitogen-associated protein kinase (MAPK), protein kinase C and a complex of proteins including cbl, caveolin and flotillin. These effectors facilitate gene transcription that regulates glycogen synthesis, glucose uptake, lipolysis, protein synthesis, cell proliferation, differentiation and survival. Moreover, as a very important function in response to insulin, glucose transporter 4 (Glut4) are transferred from intercellular compartment to cell membrane for glucose uptake. Of importance is the enhanced Glut4 mobilization to cell membrane in peripheral cells for its role in glucose uptake [45].

When obesity occurs, increased influx of FFAs to hepatocytes is oxidized for energy assumption and stored as triglyceride in liver. The fatty liver produces huge amount of very low density lipoprotein (VLDL), glucose, C-reactive protein (CRP), PAI-1, fibrinogen and coagulation factors, which are related to T2DM-associated cardiovascular disease.
accumulation, ROS production and inflammation. The influx of FFAs to these cells results in fatty tissues due to triglyceride muscles due to reduced glucose transporter GLUT4. The increased impaired glucose uptake is seen in peripheral tissues such as skeletal tissues such as skeletal muscles due to reduced glucose transporter GLUT4. The increased influx of FFAs to these cells results in fatty tissues due to triglyceride accumulation, ROS production and inflammation. 

**Animal Models Related to Obesity and T2DM**

So far, we have delineated the pathogenesis of obesity on T2DM. In this section, we will summarize the animal models developed to study obesity and T2DM in Table 4. As you may notice from the table, the gap exists between animal models, obesity and T2DM patients. More specifically, partially due to short life span, animal models could not represent the diabetes-related complications, the evolution of β cell dysfunction and failure and the strong adverse impact of obesity on β cell. These also reflect the complexity of obesity and T2DM in human subjects.

**Therapeutic Interventions of Obesity and T2DM**

In the last section, we will discuss the interventions that have been carried out in the treatment of obesity and T2DM. Up to date, the main treatments include control of diet, lifestyle improvement, exercise, anti-diabetic medicines and insulin injection. On top of that, recently, gastrointestinal bypass has been applied more and more widely to obese subjects. Hereby, we focus on medications and surgeries interventions.

**Anti-obesity medications**

**Sibutramine**: Sibutramine inhibits serotonin-nonadrenaline reuptake, promotes the feeling of satiety and decreases caloric uptake.

**Orlistat**: Orlistat is a potent gastric and pancreatic lipase inhibitor and reduces body weight. Nevertheless, its gastrointestinal side effects such as steatorrhea have been reported.

**Rimonabant**: It is by far, the first endocannabinoid CB1 receptor antagonist. Except weight loss, it decreases triglyceride level but increases HDL-cholesterol [57]. It was forced to be withdrawn in the United States for its severe side effect, i.e., the psychiatric problems.

**Metformin and thiazolidinediones**: AMP-activated protein lipase (AMPK) is a key regulator in glucose and energy homeostasis. It is ubiquitously expressed in tissues and organs. Activation of AMPK inhibits lipid and glucose metabolism via its regulation of enzymes involved in the metabolism. In details, (1) it decreases fatty acid ad cholesterol synthesis by inhibition of ACC1 and HMG-CoA; [58,59] (2) it inhibits ACC2 to stimulate fatty acid oxidation; [58] (3) it inhibits lipolysis in adipocytes; [60] (4) it up-regulates GLUT4 expression and thus enhances its translocation to cell membrane for glucose uptake; [61] and (5) it prohibits hepatic gluconeogenesis by suppressing glucose-6-phosphatase (G6Pase) [62]. Both Metformin and thiazolidinediones have been shown to activate AMPK pathway, resulting in improved glucose homeostasis. Metformin also reduces body weight possibly via its regulation of ghrelin secretion, which acts as a hunger-stimulating peptide [63]. By contrast, thiazolidinediones increases body weight.

**Glycogen-like peptide 1 (GLP-1) and GLP-1 agonist**: GLP-1 is secreted from intestinal cells in response to nutrient intake. It augments glucose-stimulated insulin secretion and reduces body weight by promoting satiety and decreasing caloric uptake [64]. Exenatide and liraglutide belong to GLP-1 agonist and share common features of GLP-1 in stimulation of insulin secretion after meal, suppression of glycogen release during meals, reduction of appetite and reduces fat content in hepatocytes [65,66]. Except its positive action on insulin secretion, increased β cell regeneration was also observed in rodents treated with GLP-1 mimetic peptide. Recent study of incretin therapy on diabetes patients has reminded us to stay cautious in incretin application. In this study, they did not detect human β cell replication when cultured with GLP-1. By contrast, because of GLP-1 receptor expression on endocrine and exocrine cells, the deleterious effect on the exocrine cells.
been shown to increase adiponectin [69] and PDX-1 [70] expression to see the reduction of BMI and obesity after GBP surgery. Except stomach, therefore, food empties slowly. Due to slow digestion, satiety OGTT test [71-73]. For instance, Buchwald et al performed a meta-analysis from 621 studies including 135246 T2DM patients. This study could be applied in early stage in T2DM patients whose BMI exceeds 35 kg/m² [68].

In 2011, International Diabetes Foundation (IDF) indicated that GBP surgery reduces stomach volume but increases the tension of GBP surgery, 62% patients were able to maintain diabetes remission [74]. Two years after GBP surgery, 62% patients were able to maintain diabetes remission [74]. In a retrospective cohort study from 9949 patients, after following-up of 7.1 years, long-term mortality in patients after GBP surgery was noticed in diabetes subjected treated with incretin, as evidenced by increased exocrine cell proliferation and dysplasia. Thus, the safety and efficacy issues remain to be investigated when using incretin.

**Repaglinide:** Repaglinide stimulates insulin release via its inhibition of ATP-sensitive potassium channels. A mild weight change was observed in patients treated with Repaglinide.

**Sitagliptin:** Sitagliptin belongs to DPP4 inhibitor. By inhibiting DPP4 enzyme activity, it enhances GLP-1 expression. Despite it does not interfere with body weight, some adverse effects of DPP4 inhibitors have been observed in clinical studies.

**Gastrointestinal bypass (GBP)**

Mason and Ito proposed GBP treatment for severe obesity in 1967 [67]. The surgery techniques have been optimized and improved by clinicians through the years. In 2009, American Diabetes Association (ADA) includes GBP as one treatment for T2DM patients with obesity. In 2011, International Diabetes Foundation (IDF) indicated that GBP could be applied in early stage in T2DM patients whose BMI exceeds 35 kg/m² [68].

GBP surgery reduces stomach volume but increases the tension of stomach, therefore, food empties slowly. Due to slow digestion, satiety increases that leads to decreased energy intake. Thus it is not surprising to see the reduction of BMI and obesity after GBP surgery. Except that, although the mechanisms are not known, GBP surgeries have been shown to increase adiponectin [69] and PDX-1 [70] expression that improve β cell function. Clinical findings from different groups have demonstrated that GBP improved glucose metabolism and insulin resistance and lowered glucose level both in fasting state and OGTT test [71-73]. For instance, Buchwald et al performed a meta-analysis from 621 studies including 135246 T2DM patients. This study showed that GBP surgery resulted in 78.1% patients with complete remission, 86.6% patients with improved conditions. Two years after surgery, 62% patients were able to maintain diabetes remission [74].

In a retrospective cohort study from 9949 patients, after following-up of 7.1 years, long-term mortality in patients after GBP surgery was significantly reduced compared with control group [75]. However, the data of long-term effect of GBP is still very limited and therefore, it is dispensable to obtain the long-term data to assess the effect of GBP on obesity and T2DM.

<table>
<thead>
<tr>
<th>Models</th>
<th>Animal species</th>
<th>Pathogenesis basis</th>
<th>phenotypes</th>
<th>Possible drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptozotocin in combination of fat diet [89,90]</td>
<td>Mouse, rat</td>
<td>Induced β cell damage</td>
<td>Hyperglycemia; obesity; reduced insulin secretion</td>
<td>Severe β cell damage and high mortality</td>
</tr>
<tr>
<td>Ob/ob (always in combination with high fat diet) [91]</td>
<td>Mouse</td>
<td>Leptin deficiency</td>
<td>obesity; Hyperglycemia and hyperinsulinemia; Developed peripheral neuropathy</td>
<td>No insulin insufficiency</td>
</tr>
<tr>
<td>DB/DB [92]</td>
<td>Mouse</td>
<td>Leptin receptor deficiency</td>
<td>obesity; Hyperglycemia and hyperinsulinemia; Developed peripheral neuropathy</td>
<td>β cell hyperplasia; No insulin insufficiency; reduced life span</td>
</tr>
<tr>
<td>Zucker (fa/fa) [93]</td>
<td>Rat</td>
<td>Leptin receptor deficiency</td>
<td>Body weight increase; Insulin resistance</td>
<td>No obvious hyperglycemia</td>
</tr>
<tr>
<td>KK-Ay (always in combination with high fat diet) [94]</td>
<td>Mouse</td>
<td>A glycoprotein gene mutation</td>
<td>Obesity; hyperglycemia; Insulin resistance; islet cell hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Goto Kakizaki (GK) [95,96]</td>
<td>Rat</td>
<td>Highest level of glucose challenge over many generations</td>
<td>resistance and impaired secretion; renal lesion, retina abnormality and nerve changes comparable to T2DM complications in human</td>
<td>relatively slim; no decreased β cell mass</td>
</tr>
<tr>
<td>NSY [97]</td>
<td>Mouse</td>
<td>Derived from NOD mice with spontaneously developed T2DM</td>
<td>Mild insulin resistance; impaired insulin secretion</td>
<td>No obesity; gender difference</td>
</tr>
<tr>
<td>OLETF [98]</td>
<td>Rat</td>
<td>Selective for glucose tolerance</td>
<td>Obesity; Impaired glucose tolerance; Developed non-alcoholic fatty liver disease</td>
<td>Genetic variance that may have no causal relationship to diabetes itself</td>
</tr>
<tr>
<td>lrs1-/- lrs3-/- [99,100]</td>
<td>Mouse</td>
<td>Deficiency of insulin receptor substrate 1 and 3</td>
<td>Increased body weight; Hyperglycemia; hyperinsulinemia; Insulin resistance</td>
<td>No fatty liver</td>
</tr>
</tbody>
</table>

Table 4: Animal models of obesity and T2DM.

Summary

The increasing incidence of obesity and diabetes has drawn more and more attention not only in disease treatment but also in disease prevention. Understanding the adverse effects of obesity on diabetes and the severity of obesity and diabetes will increase our awareness in improving diet control, lifestyle, exercise and medications against obesity and diabetes. To be addressed, there are many unsolved issues from basic to clinical research. For instance, better animal models are required to represent diabetes development and complications in humans. It still needs to define whether combinations of several medications will achieve better therapeutic effect and lower side effect than solo medication. Despite targeting obesity has shown successful and beneficial effect in diabetes patients, its long-term effect on diabetes waits for further investigations.

References


