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Treating Diabetes and Prediabetes by Focusing on Obesity Management

Lalita Khaodhriar, MD, Sue Cummings, MS, RD, LDN, and Caroline M. Apovian, MD

Abstract

Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes mellitus (T2DM). In obesity, the adipose cell releases non-esterified free fatty acids, hormones, adipocytokines, and other substances that are involved in insulin resistance. Under normal conditions, the pancreatic islet β cells increase production of insulin sufficiently to maintain normal blood glucose concentrations despite insulin resistance. However, in genetically predisposed patients, the β cells eventually become dysfunctional and T2DM develops. The development of T2DM can be delayed or sometimes prevented in individuals with obesity who are able to lose weight. Weight loss can be achieved medically with behavioral therapies that combine diet and exercise treatment or with behavioral therapies combined with weight-loss medications or weight-loss surgery. In this article, we summarize the evidence of obesity management in treating T2DM and prediabetes.

Introduction

According to the US Centers for Disease Control and Prevention, rates of type 2 diabetes mellitus (T2DM) have tripled in the past 30 years. This is caused largely by the global epidemic of obesity, a major risk factor for developing T2DM and prediabetes. Diabetes now affects an estimated 23.6 million people in the United States; another 57 million have prediabetes. Prediabetes raises short-term absolute risk of T2DM five- to sixfold. The development of T2DM can be delayed or sometimes prevented in individuals with obesity who are able to lose weight. In T2DM patients, weight loss improves glycemic control and cardiovascular disease risk factors. This can be achieved medically with behavioral therapies that combine diet and exercise treatment or with behavioral therapies combined with weight-loss medications or weight-loss surgery. There is strong evidence of an amelioration or resolution of T2DM in patients undergoing gastric bypass surgery [1,2]. Additionally, a large prospective cohort study indicated that long-term total mortality from cardiovascular and noncardiovascular diseases after gastric bypass surgery was significantly reduced [3].

Obesity and Type 2 Diabetes Mellitus

Adipose tissue, previously viewed as a storage depot, is now recognized as a major endocrine and secretory organ. It releases a wide range of protein factors and signals termed *adipokines*, many of which have been linked to a state of inflammation and the impairment

Corresponding author: Caroline M. Apovian, MD, Boston University School of Medicine, Center for Nutrition and Weight Management, Boston Medical Center, 88 East Newton Street, Robinson 4400, Boston, MA 02118, USA. Caroline.apovian@bmc.org.

Disclosure

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of insulin sensitivity. The increased production of inflammation-related adipokines, such as tumor-necrosis factor- α and interleukin (IL)-6, is considered to play an important role in the development of T2DM and the metabolic syndrome associated with obesity [4,5].

Because obesity causes insulin resistance, there is no doubt that any intervention that produces weight loss will improve insulin sensitivity. A reduction of fat mass that occurs with weight loss results in a reduction of lipid oxidation and an enhancement of glucose metabolism [6]. Insulin secretion and plasma insulin concentrations have been shown to decrease significantly after weight loss. Aerobic and resistance exercises can improve skeletal muscle glucose uptake and disposal [7].

Effects of Weight Loss on Type 2 Diabetes Mellitus

Lifestyle modification

In individuals with obesity, weight loss produced by diet and/or exercise improves insulin sensitivity and reduces blood glucose levels in individuals with diabetes and nondiabetic individuals. Initiation of a hypocaloric diet frequently improves hyperglycemia, an outcome that suggests a beneficial effect from restricted caloric intake independent of weight loss [8,9].

Moderate weight loss in obese patients with T2DM can significantly improve glycemic control, as shown by a reduction in hemoglobin A_{1c} (HbA_{1c}) level; some patients are able to discontinue insulin or oral therapy [10,11]. However, the response to diet and exercise varies widely among individuals with T2DM. A 48-month retrospective study of 135 patients on diet therapy indicated that only 41% of those who lost at least 9.1 kg had plasma glucose concentration below 10 mmol/L [12]. Nevertheless, some of these individuals decreased their plasma glucose levels after losing only 2.3 kg. Improvements in glycemic control occurred early in the course of weight loss; patients who remained hyperglycemic after reductions of 2.3 to 9.1 kg were unlikely to improve with additional weight loss. Preservation of the capacity of β cells to secrete insulin has been shown to be the important factor predicting the blood glucose-lowering effect of diet in obese T2DM patients [13••].

The benefits of weight loss in T2DM patients may be long lasting. In a recent retrospective cohort conducted in 2500 adults with a new onset of T2DM, 76% of patients maintained their weight, 12% gained weight, and another 12% lost weight in an 18-month period. In the weight-loss group, patients dropped an average of 10.7 kg (10%), and although at the 36-month mark most patients had gained back the weight, they still showed better control of their blood pressure and blood sugar levels than those patients who had gained or even maintained weight [14]. In addition to benefits of weight loss in diabetes treatment, studies have consistently shown that modest weight reduction is effective in preventing type 2 diabetes. In the FDPS, a diet and exercise program produced a 58% reduction in diabetes compared with control [15]. The US DPP, a randomized clinical trial of more than 3200 overweight subjects at high risk for diabetes (ie, impaired glucose tolerance), also showed a 58% reduction in diabetes from 11% per year in the control group to 4.8% per year in the lifestyle modification group, which lost 5% to 7% of their initial body weight [16].

The American Diabetes Association recommends that individuals with T2DM who are overweight or have obesity, lose a modest amount of weight (5% to 7%) via structured programs that emphasize lifestyle changes, including education, reduced energy and fat (30% of total energy) intake, regular physical activity, and regular participant contact [17]. However, the data on sustained weight loss following lifestyle modifications indicate poor long-term outcomes [18,19]. Successful long-term, sustained weight loss for individuals

with obesity may require medical interventions such as weight-loss medications or weight-loss surgery.

Weight-loss medications

Currently, there are only a few US Food and Drug Administration (FDA)–approved medications for weight loss. These medications fall in the category of US Drug Enforcement Administration schedule IV, which are medications that have low abuse potential with few side effects [20]. Of these medications, phentermine and diethylpropion are only approved for short-term use (12 weeks); longer use of these medications is off-label. FDA-approved medications for long-term weight loss must show safety and efficacy for 2 years or more. Currently, sibutramine and orlistat are approved for long-term use, and, most recently, Alli (GlaxoSmithKline, Research Triangle Park, NC) was approved for over-the-counter purchase at half the dose of the prescription medication. The effect of these medications on weight loss is modest. However, weight-loss medications, which have generally been studied along with lifestyle modification programs that incorporate diet and physical activity, result in more weight loss than lifestyle modification alone [21]. Thus, medications may be an appropriate adjunct to behavioral therapies for long-term sustained weight loss.

Phentermine, the “phen” component of the combination drugs known as fen/phen, is still available for prescription and is commonly prescribed today. In a meta-analysis of weight-loss medications, phentermine exhibited modest but significant weight losses [22]. However, the use of phentermine in patients with metabolic syndrome may be limited, as this is a noradrenergic medication with possible side effects, including increased blood pressure and heart rate. All patients should have their heart rate and blood pressure monitored while on this medication.

Sibutramine, a new noradrenaline and 5-hydroxytryptamine reuptake inhibitor, has been shown to produce a dose-related weight loss in obese subjects, with optimal doses of 10 to 15 mg/d to be increased up to a maximal dose of 20 mg/d. Sibutramine, similar to phentermine, has a low-risk side-effect profile; however, blood pressure and heart rate should be closely monitored because of the adrenergic component of this medication. In patients with T2DM, sibutramine-induced weight loss is accompanied by a shift toward improved metabolic control and the reduction in fasting plasma glucose is proportional to the degree of weight loss [23].

A meta-analysis of eight placebo-controlled, double-blinded, randomized trials of sibutramine in patients with T2DM showed that sibutramine treatment significantly decreased body weight and waist circumference when compared with the placebo group. Fasting blood glucose and HbA_{1c} were significantly improved after sibutramine treatment. Treatment benefits were also seen in plasma triglycerides and high-density lipoprotein (HDL), without significant variations in serum total and low-density lipoprotein (LDL) cholesterol. No differences in systolic blood pressure between the sibutramine and the placebo groups were seen, whereas diastolic blood pressure and heart rate were slightly increased in the sibutramine group [24]. In another meta-analysis of four trials, including 391 patients with diabetes, the data showed a 3.3% weight loss over 12 to 26 weeks and a 0.7% decrease in HbA_{1c} with sibutramine [25]. Changes in plasma glucose levels observed on sibutramine and placebo were similar for the same degree of weight loss, suggesting an indirect rather than a direct action of the medication on glucose metabolism. A study using the hyperinsulinemic clamp demonstrated a similar improvement in insulin sensitivity in obese T2DM patients after a comparable weight loss of about 5 kg obtained with sibutramine or placebo.

Orlistat is a potent and selective gastric and pancreatic lipase inhibitor that works strictly in the gut to inhibit the absorption of dietary fat. Side effects of this medication include oily stool. Recently, the FDA approved the over-the-counter weight-loss medication Alli, which is a half-dose (60-mg) version of orlistat. These medications are taken at each meal. It is recommended that patients taking these medications also take a daily supplement of the fat-soluble vitamins A, D, E, and K.

A large, multicenter, 57-week, randomized controlled study examined the effects of 120 mg of orlistat three times daily in combination with a hypocaloric diet in adult patients on sulfonylurea treatment. There was significant improvement in the intervention groups in glycemic control, as reflected in decreases in HbA_{1c} (−0.28% vs 0.18%), fasting plasma glucose (−0.47 vs 0.36 mmol/L), and in dosage reductions of oral sulfonylurea medications (−23% vs −9%) [26]. Several lipid parameters also improved, including total cholesterol, LDL cholesterol, triglycerides, apolipoprotein B, and the LDL-to-HDL cholesterol ratio. Mild to moderate and transient gastrointestinal side effects were reported with the orlistat group, although their association with study withdrawal was low. Similar outcomes were also reported in patients with T2DM who have suboptimal metabolic control with insulin therapy alone, with insulin in combination with oral agents [27], or with metformin [28].

In a Latin-American trial, a 24-week treatment of orlistat was accompanied by a decrease in fasting plasma glucose, postprandial glucose, and a mean decrease in HbA_{1c} [29]. A meta-analysis of four randomized studies showed that orlistat produced a 2.6% weight loss in patients with diabetes and decreased HbA_{1c} by 0.4% [30]. A study comparing orlistat and sibutramine in patients with obesity and T2DM showed that the two agents produced similar improvement in HbA_{1c}, fasting plasma glucose, and postprandial plasma glucose. However, sibutramine treatment was generally better tolerated than orlistat [31].

The XENDOS study is a large, randomized, double-blind, prospective study that involved 3305 obese patients with normal (79%) or impaired (21%) glucose tolerance [32]. The participants were randomly assigned to lifestyle changes plus orlistat, 120 mg, or placebo, three times daily. After 4 years of treatment, the cumulative incidence of type 2 diabetes was 9.0% in the placebo group and 6.2% in the orlistat group, corresponding to a risk reduction of 37.3%. The incidence of diabetes was low and not significantly different in the two treatment arms of the study in those patients with normal glucose tolerance at baseline. However, in patients with impaired glucose tolerance, the conversion to T2DM was significantly greater in the placebo group than in the orlistat-treated group. This benefit may be because of the weight loss itself, to the limited absorption of lipids and reduction of plasma free fatty acids, to increased production of incretins, or to modulation of secretion of cytokines by adipocytes, all effects secondary to orlistat treatment [33].

Rimonabant, a selective cannabinoid-1 receptor blocker, has been approved in many European countries as an antiobesity drug. However, in 2007, the US FDA denied approval in the United States because of concern over “increased frequencies of psychiatric adverse effects,” including suicide and seizures. In a study of more than 1000 patients on metformin or sulfonylurea monotherapy, with type 2 diabetes and body mass index (BMI) ranging from 27 to 40 kg/m² and HbA_{1c} ranging from 6.5% to 10%, patients were given a hypocaloric diet and advice for increased physical activity [34]. They were then randomized to receive a placebo or a 5- or 20-mg/d dose of rimonabant for 1 year. Weight loss was significantly greater after 1 year in the two rimonabant groups than in the placebo group (−2.3 kg for the 5-mg/d group and −5.3 kg for the 20-mg/d group vs −1.4 kg for the placebo). An improvement in HbA_{1c} was also observed in both treatment groups (−0.1% for the 5-mg/d group, −0.6% for the 20-mg group vs 0.1% for the placebo group). Improvements in fasting blood glucose, HDL cholesterol, triglyceride, and non-HDL cholesterol were reported only

in the 20-mg/d rimonabant group. More patients in the high-dose rimonabant group reached an HbA_{1c} target of less than 7% (51% for the 5-mg group, 68% for the 20-mg group vs 48% for the placebo group). The incidence of adverse events that led to discontinuation of the study was slightly greater in the high-dose rimonabant group, mainly due to depressed mood disorders, nausea, and dizziness.

Several antidiabetic medications have been shown to affect body weight and some are being targeted for possible antiobesity therapy. Metformin, a biguanide compound that improves insulin sensitivity, produces modest weight loss (1% to 2%). Glucagon-like peptide-1 (GLP-1), peptide YY, and oxyntomodulin are believed to act with other postprandial gastrointestinal signals such as gastric distention to promote satiety and meal termination [35]. The protease-resistant GLP-1 congener exenatide has been approved for treating type 2 diabetes. In clinical diabetes trials, it also caused modest weight loss (3%). Amylin, a peptide cosecreted with insulin from pancreatic β cells, inhibits gastric emptying and glucagon secretion, and decreases meal size and food intake. Pramlintide is an injectable synthetic analogue of the hormone amylin that is approved as an adjunct therapy in patients with type 1 and type 2 diabetes mellitus who fail to achieve optimal glucose control despite insulin therapy. In a 1-year study of pramlintide in patients with T2DM, patients lost 0.4 kg compared with an 0.8-kg weight gain in the placebo group [36].

Weight-loss surgery

Surgical procedures are characterized as 1) purely restrictive (laparoscopic adjustable gastric band [LAGB]); 2) gastric restriction with some malabsorption (the Roux-en-Y gastric bypass [RYGBP]); or 3) gastric restriction with significant intestinal malabsorption (biliopancreatic diversion without or with duodenal switch [BPD/BPDDS]). The most common weight-loss surgical procedures performed in the United States today are the RYGBP and the LAGB procedures.

RYGBP surgery is a restrictive procedure that causes malabsorption of micronutrients, not macronutrients. The exact mechanisms for weight loss are not known; however, weight loss is most likely because of a combination of restriction and changes in neural and hormonal pathways. The RYGBP procedure involves creating a small gastric pouch at the top of the stomach; the jejunum is divided 30 to 50 cm distal to the ligament of Treitz, the distal limb of the jejunum is then anastomosed to the small gastric pouch, and a jejunojejunostomy is performed 50 to 150 cm distal from the gastrojejunostomy. Most gastric bypass studies report a weight loss of 60% to 70% of excess body weight (30% to 35% of total body weight). In a meta-analysis of 4204 gastric bypass patients, mean excess body weight lost was reported as 68% (35% of initial weight) [36].

Evidence exists of resolution of T2DM in some individuals, after the gastric bypass procedure, leaving some to suggest surgery as a cure [37]. Two published studies by Schauer et al. [1] and Sugerman et al. [2] reported resolution in 83% and 86% of patients, respectively. At 2-year follow-up, a 60% decrease in plasma insulin and a 20% decrease in plasma glucose were seen in the surgical weight-loss group in the SOS study [38].

LAGB surgery is a purely restrictive procedure that reduces the stomach's volume by placing a band around the top part of the stomach, creating a small pouch; the proximal foregut is not bypassed. A port is placed under the skin that is tethered to the band by tubing that allows access for regular fills (adjustments) of the band. Placing the LAGB is a less invasive procedure than the RYGBP, which makes it an attractive option for many patients. However, the reoperation rate is higher from complications, such as band slippage or erosion. In a recent review of three meta-analyses of over 28,000 patients who had

undergone gastric banding, the mean weight loss was 50% of excess body weight (~ 25% of initial weight loss) [39,40].

Resolution of diabetes is more prevalent after gastric bypass than in gastric banding, 78% for gastric bypass and 50% for gastric banding [41,42••]. In the meta-analysis of weight-loss surgeries conducted by Buchwald et al. [37], evidence of improvement in T2DM and impaired glucose tolerance was found across all bariatric surgeries. Diabetes was completely resolved in 76.8% of patients, and resolved or improved in 86%. The meta-analysis data showed slower weight loss and less improvement in comorbidities, including diabetes, after the LAGB compared with the RYGBP. Operative mortality was less than 0.5% for both procedures. Perioperative complications were more common with RYGBP (9% vs 5%), although long-term reoperation rates were lower after RYGBP (16% vs 24%). Patient satisfaction favored gastric bypass [42••].

Mechanisms

Although it has been a long-held belief that weight loss and decreased food intake are the mechanisms for remission of diabetes after weight-loss surgery, resolution of diabetes often occurs days after RYGBP surgery, before any significant weight loss occurs [43]. Resolution or improvement after gastric bypass surgery may be related to metabolic and hormonal changes that occur.

Insulin resistance and loss of glucose-stimulated acute insulin response (AIR) are the two major and earliest defects in the course of T2DM. Studies have shown that weight loss after bariatric surgery in patients with obesity and T2DM restored euglycemia in parallel with the normalization of insulin sensitivity, the reappearance of a normal AIR to glucose, and the restoration of a normal relationship of AIR to insulin sensitivity as early as 3 months after RYGBP and 1 month after BPD when patients are still obese [44,45]. These results show that the loss of glucose-induced AIR in the patients with obesity and T2DM of mild or moderate severity is not permanent but reversible.

Faraj et al. [45] examined the change in adipose tissue hormones, acylation-stimulating protein (ASP), leptin, and adiponectin as a predictor for the amelioration of the metabolic and cardiovascular risk factors after weight-loss surgery. ASP increases glucose uptake and fatty acid esterification in a manner that is independent of but additive to insulin. The concentration of ASP is elevated in obesity, T2DM, and coronary artery disease. A total of 86% of their 50 patients had elevated preoperative plasma ASP concentrations, which decreased postoperatively. However, because most subjects were still obese even after significant weight loss, the average concentrations remained higher than normal. Leptin, a hormone secreted by fat cells that acts via hypothalamic receptors to inhibit feeding and increase thermogenesis, decreased postoperatively in almost all subjects, which is consistent with the decrease of body fat. Adiponectin is one of the most abundant adipose tissue-specific factors and functions as a mediator of insulin sensitivity and an enhancer of fatty acid oxidation. Low adiponectin levels are associated with risk factors for coronary artery disease. In this study, adiponectin increased in response to weight loss after RYGBP surgery in almost all subjects, and mean adiponectin levels were normal in all postoperative subjects. This study's overall findings suggest that preoperative fasting adiponectin concentrations are predictive of the extent of weight loss, and, changes in ASP and adiponectin improve insulin action.

Kellum et al. [46] examined the gastrointestinal hormone responses to meals in patients before and after RYGBP and vertical banded gastroplasty (VBG). VBG was the most common procedure done in the United States in the early 1980s. VBG, similar to LAGB, is a purely restrictive procedure. VBG patients had lesser reductions of hyperglycemia and

hyperinsulinemia. The cholecystokinin, serotonin, and vasoactive intestinal peptide responses to meals were not altered by RYGBP or VBG. However, the enteroglucagon response to glucose increased markedly in gastric bypass patients after the operation. The increase in enteroglucagon occurred at the same time as development of dumping syndrome, which occurred exclusively in gastric bypass patients [47].

More recently, the improvement in incretin secretion has been postulated to be responsible for diabetes outcome after gastric bypass. Incretins, particularly gastric inhibitory peptide and GLP-1, are gut peptides that stimulate insulin secretion postprandially. le Roux et al. [48] reported that patients following RYGBP had increased postprandial plasma peptide YY, and GLP-1 favoring enhanced satiety, when compared with lean and obese controls. Also, RYGBP patients had early and exaggerated insulin responses, potentially mediating improved glycemic control. None of these effects were observed in patients losing equivalent weight through gastric banding [48]. Recent studies have consistently shown greater release in incretin GLP-1 and gastric inhibitory peptide levels early after RYGBP; the effect was not seen after weight loss with diet [49,50••]. Ghrelin is another enteric peptide with strong orexigenic and adipogenic effects. Plasma ghrelin levels are decreased in obese subjects and increase after weight loss with diet and gastric banding. In contrast, plasma ghrelin levels fail to increase during substantial weight loss after RYGBP, suggesting that the plasma ghrelin response after weight loss is impaired after exclusion of major parts of the stomach and the duodenum (RYGBP), and the smaller long-term weight loss after gastric banding compared with RYGBP may be caused, at least in part, by an absent increase in plasma ghrelin after RYGBP [51].

Bariatric Surgery: Morbidity and Mortality in Patients With Type 2 Diabetes Mellitus

Pories et al. [41] compared a group of patients with type 2 diabetes who underwent gastric bypass with a non-surgical control group. The two groups were compared retrospectively to determine differences in survival and the need for medical management of their diabetes [41]. The mean glucose levels in the surgical group fell from 187 mg/dL preoperatively, and remained less than 140 mg/dL for up to 10 years of follow-up. The percentage of control subjects being treated with oral hypoglycemics or insulin increased from 56.4% at initial contact to 86.5% at last contact (mean length of follow-up for the control group was 6.2 years). The percent of surgical patients requiring medical management fell from 31.8% preoperatively to 8.6% at last contact (mean follow-up for surgical patients was 9 years). The mortality rate in the control group was 28% compared with 9% in the surgical group. For every year of follow-up, patients in the control group had a 4.5% chance of dying versus a 1% chance for those in the surgical group [52]. The improvement in mortality rates was primarily from the decrease in the number of cardiovascular deaths, which is the primary cause of morbidity and mortality in patients with T2DM who have obesity.

Obesity and obesity-associated T2DM are frequently related to a low-grade chronic inflammatory state, which has been consistently shown to increase the risk of developing cardiovascular diseases. A study of patients at different stages of glucose tolerance before and 14 months after banded gastroplasty surgery demonstrated a significant reduction in the levels of C-reactive protein (CRP) (a liver-derived reporter that increased when inflammatory cytokines are increased) and IL-6 (a proinflammatory cytokine) by as much as 81% and 23%, respectively, compared with baseline levels [53]. In a study of 65 morbidly obese patients undergoing RYGBP, surgery significantly lowered IL-18, soluble tumor necrosis factor- α receptors, and CRP at 12 months [54]. Holdstock et al. [55] reported that at 12 months after RYGBP, CRP, serum amyloid A, and IL-6 levels decreased by 82%, 57%, and 50%, respectively. However, the reduction in CRP was more pronounced in insulin-

sensitive patients. At 12 months, 140% and 40% reductions in CRP were seen in subjects with homeostasis model assessment (HOMA) less than 4 (insulin sensitive) and HOMA greater than 9 (insulin resistant) despite similar reductions in BMI [55]. Similarly, Whitson et al. [56] noticed at 6 months postoperation, RYGBP significantly altered most adipokine levels they were interested in (adiponectin, resistin, tumor-necrosis factor- α , and leptin) for nondiabetic patients. Nevertheless, only CRP and leptin were changed in diabetic patients [57]. Thus, present studies show that surgery-induced weight loss reduces circulating concentrations of key proinflammatory factors, which may contribute to the improvement in the cardiovascular comorbidity following excess weight loss. However, these changes are less pronounced in the most insulin-resistance patients, suggesting early intervention is key.

Conclusions

It is important to note the progressive nature of pre-diabetes and T2DM when obesity is not treated. In an earlier study reported by Pories et al. [41], older patients who had diabetes 3 years longer on average failed to become euglycemic after gastric bypass, suggesting that T2DM is a progressive disease that becomes more irreversible with time. Gastric bypass can prevent the progression of this disease in most patients if it is performed in a timely fashion, before irreversible destruction of the function of the islet cells.

Health care providers should continue to evaluate for risks and/or presence of T2DM and to offer behavioral treatment, including diet and physical activity therapies. However, when these therapies alone are not enough, behavioral programs should be provided in conjunction with weight-loss medications or bariatric surgery therapies. Surgical options are appropriate in patients with high BMIs ($> 35 \text{ kg/m}^2$) and T2DM who have not been able to lose significant amounts of weight to ameliorate their diabetes through lifestyle interventions alone or lifestyle interventions combined with weight-loss medications. Research is ongoing to elucidate the link between gut hormones and the amelioration of T2DM after bariatric surgery. This research will most likely lead to the development of effective, safe, and long-term pharmacotherapies for the treatment of T2DM in obese patients.

Clinical Trial Acronyms

DPP	Diabetes Prevention Program
FDPS	Finnish Diabetes Prevention Study
SOS	Swedish Obesity Subjects
XENDOS	Xenical in the Prevention of Diabetes in Obese Subjects

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