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Diabetes obesity link: how to lower your risk of diabetes with weight management

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Increasing overweight and obesity are major risk factors for the development of type 2 diabetes. The risk is higher when the weight gain occurs during adulthood. In fact, evidence shows that body mass index (BMI) is directly and continuously related to the risk of type 2 diabetes. Individuals with upper body obesity are at high risk for hyperinsulinemia, insulin resistance, and type 2 diabetes. According to the US Centers for Disease Control and Prevention, rates of type 2 diabetes have tripled in the past 30 years. This is caused largely by the rapid rise in the rate of obesity, a major risk factor for developing type 2 diabetes and pre-diabetes. Over the last decade, there has been a rapid escalation in the prevalence of obesity, one that parallels the equally rapid increase in type 2 diabetes. The development of type 2 diabetes can be delayed or sometimes prevented in individuals with obesity who are able to lose weight. In type 2 diabetes, weight loss improves glycemic control and cardiovascular disease risk factors. Strategies to decrease the risk of type 2 diabetes include behavior therapies in combination with healthy lifestyle changes, optimizing medication for weight neutral effect, anti-obesity medication, and weight loss surgeries.

Increasing overweight and obesity are major risk factors for the development of type 2 diabetes.[1-3] A large body of evidence exists that attests to the relationship between excess weight and an increased risk of development of type 2 diabetes.[4,5] The risk increases with the degree of excess weight, increasing 3-fold with a body mass index (BMI) of 25.0-29.9 kg/m^2 and 20-fold with a BMI $>$30 kg/m^2, which is the "obese" category.[6] The risk is also higher when the weight gain occurs during adulthood.[7,8] Evidence shows that BMI is directly and continuously related to the risk of type 2 diabetes.[9] Individuals with upper body obesity are at high risk for hyperinsulinemia, insulin resistance, and type 2 diabetes.[10]

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According to the US Centers for Disease Control and Prevention, rates of type 2 diabetes have tripled in the past 30 years.[11] This is caused largely by the rapid rise in the rate of obesity, a major risk factor for developing type 2 diabetes and pre-diabetes. Over the last decade, there has been a rapid escalation in the prevalence of obesity, one that parallels the equally rapid increase in type 2 diabetes. In 2009, all states continued to have a high prevalence of obesity among adults, although the prevalence varied geographically. No state met the Healthy People 2010 target of 15%, and the number of states with obesity prevalence of $\geq$30% increased from none in 2000 to nine in 2009.[12]

The current pandemic of type 2 diabetes and obesity has created an urgent need to identify effective therapeutic interventions targeting both of these chronic debilitating conditions. Obesity and diabetes are closely interrelated in that risk factors such as physical inactivity and poor diet lead to weight gain and precipitate insulin resistance in important insulin-sensitive tissues, particularly in skeletal muscle, the

liver, and adipose tissue. It is known that obese and insulin-resistant diabetic patients have a positive energy balance, high fat and high carbohydrate intake, increased abdominal adipose tissue, elevated free fatty acids, increased secretory products of adipocytes mediating inflammation including tumor necrosis factor (TNF)-α and interleukin (IL)-6, and reduced secretion of adiponectin.[13]

The coexistence of type 2 diabetes and obesity presents a complex therapeutic challenge. Type 2 diabetes confers an elevated risk of developing a broad range of complications, including macrovascular disorders (eg, cardiovascular disease, stroke) and microvascular disease (eg, retinopathy, neuropathy, and nephropathy).[14] Likewise, obesity increases the risk of a myriad of chronic diseases, including type 2 diabetes, coronary heart disease, hypertension, hyperlipidemia, stroke, and certain cancers.[15] Obesity is linked to the development of additional comorbidities that can further complicate disease management, including mobility problems associated with osteoarthritis, obstructive sleep apnea, and clinical depression.

Given the strong relationship between type 2 diabetes and obesity, prevention of weight gain should be the cardinal focus in treatment strategies. In type 2 diabetes, weight loss improves glycemic control and cardiovascular disease risk factors. Strategies to decrease the risk of type 2 diabetes include behavior therapies in combination with lifestyle changes, weight loss medications and weight loss surgeries.

Adipocytes and type 2 diabetes

Adipocytes are not simply storage reservoirs of fat but they are active endocrine organs that play multiple roles in body. Adipose tissue is currently known to secrete a large number of proteins termed *adipokines* that act in an autocrine, paracrine, or endocrine fashion to control various metabolic functions.[16] These *adipokines* have been linked to a state of inflammation and the impairment of insulin sensitivity. When compared with lean individuals, adipose tissue in obese individuals shows higher expression of proinflammatory proteins, including TNF-α and IL-6. Macrophage numbers in adipose tissue also increase with obesity. Macrophage accumulation and the subsequent local inflammation are believed to result in numerous metabolic dysfunctions that accompany obesity, including systemic inflammation and atherosclerosis.[17] Visceral fat secretes more cytokines than subcutaneous adipose tissue.[18] Macrophages within visceral adipose tissue are known to express and release cytokines. These cytokines reach the liver though the portal circulation, where they can stimulate hepatic inflammation,[19] thereby inducing a chronic systemic inflammatory response. A reduction of fat mass that occurs with weight loss results in a reduction of lipid oxidation and an enhancement of glucose metabolism.[20]

Weight management for diabetes

Counseling patients on lifestyle modifications should be the first line of defense. There is also a great need for safe and efficacious drugs to treat obesity. The only drug currently approved for long-term obesity management—orlistat—provides only modest weight-loss benefits. Very-low-calorie diets can be effective if supervised by a physician and followed correctly but their duration is inevitably short-term. The bariatric surgical procedure of gastric banding becomes the next option to consider. It should be preferred ahead of other bariatric procedures because it is minimally invasive, has a better safety profile than other procedures, and is potentially reversible.

Lifestyle modification

The American Diabetes Association recommends that individuals with type 2 diabetes who are overweight or obese lose a modest amount of weight (5-7%) via structured programs that emphasize lifestyle changes.[21] Elements of lifestyle changes include behavioral changes to control the stimuli that activate eating and slowing down the rate of eating, nutritional counseling to control intake of calories, modification of physical activity, social support, and problem solving. However, the data on sustained weight loss after lifestyle modifications indicate poor long-term outcomes.[22] The benefits of weight loss in type 2 diabetes patients may be long-lasting. In the 2.8 years of the Diabetes Prevention Program (DPP) randomized clinical trial, diabetes incidence in high-risk adults was reduced by 58% with intensive lifestyle intervention.[23] In a recent retrospective cohort conducted in 2500 adults with new-onset type 2 diabetes, 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 re-gained 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.[24]

Sustained caloric restriction (to 1500 kcal/d for women and 1800 kcal/dfor men), regardless of dietary macronutrient composition or regimen, has fairly similar effects on weight loss, ranging from about 6.6-11 lbs (3-5 kg) over two years.[25] Initiation of a low-calorie diet frequently improves hyperglycemia, an outcome that suggests a beneficial effect from restricted caloric intake independent of weight loss.[26]

Weight loss medications

Currently available medications to treat obesity are limited in number and efficacy. Most of those drugs work in the central nervous system and in the gastrointestinal tract. The effects of these medications on weight loss are modest. However, weight loss medications along with lifestyle mod-

ification programs that incorporate diet and a physical activity program, result in more weight loss than lifestyle modification alone.[27] Thus, medications can be a useful adjunct to lifestyle therapies for long-term sustained weight loss.

Drugs approved by the US Food and Drug Administration for the treatment of obesity

At present, there are three sympathomimetic amphetamine-like drugs still approved by the US Food and Drug Administration (FDA) as weight-loss adjuncts: phentermine, diethylpropion, and phendimetrazine. They are approved for short-term use (12 weeks) only and thus have limited use in the long-term management of obesity.[28] FDA-approved medications for long-term weight loss must show safety and efficacy for 2 years or more. With the recent withdrawal of sibutramine from the market in October 2010 because of clinical trial data indicating an increased risk of heart attack and stroke, at present there is only one drug licensed in the US for long-term treatment of obesity—orlistat.

Sympathomimetic drugs

The sympathomimetics drugs diethypropion, phendimetrazine, and phentermine are grouped together because they act like norepipherine and were tested before 1975. In a meta-analysis of weight loss medications, phentermine exhibited modest but significant weight loss.[29] Sympathomimetic drugs produce insomnia, dry mouth, asthenia, and constipation. Blood pressure and heart rate should also be monitored while taking these medications. Weight loss with phentermine and diethylpropion persists for the duration of treatment, suggesting that tolerance does not develop to these drugs.

Orlistat

Orlistat is a potent and selective gastric and pancreatic lipase inhibitor that works strictly in the gut to inhibit the absorption of dietary fat. The XENDOS study is a large, randomized, double-blind, prospective study that involved 3305 obese patients with normal (79%) or impaired (21%) glucose tolerance.[30] The participants were randomly assigned to lifestyle changes plus orlistat 120 mg or placebo three times daily. After four 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%. In patients with impaired glucose tolerance, the conversion to type 2 diabetes 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.[31] When patients are using orlistat, it is recommended that they take a multivitamin daily with emphasis of fat-soluble vitamins (A, D, E, K) because they may not be adequately absorbed from diet because of this medication.

Rimonabant

Rimonabant, a selective cannabinoid-1 receptor blocker, has been approved in many European countries as an anti-obesity drug. However, in 2007, the FDA denied approval in the US because of concern over "increased frequencies of psychiatric adverse effects," including suicide and seizures.[32] In a study of more than 1000 patients on metformin or sulfonylurea monotherapy, with type 2 diabetes and BMI ranging from 27-40 kg/m^2 and HbA1c ranging from 6.5-10%, patients were given a hypocaloric diet and advice for increased physical activity. They were then randomized to receive a placebo or a 5- or 20-mg/d dose of rimonabant for one year. Weight loss was significantly greater after one year in the two rimonabant groups vs. 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 HbA1c 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).[33] The incidence of adverse events that led to discontinuation of the study was slightly greater in the high-dose rimonabant group, mainly because of depressed mood disorders, nausea, and dizziness.

New drugs on the horizon

Several new pharmacologic agents have been examined in late-stage clinical trials. They include locaserine, a naltrexone-bupropion combination, and a phentermine-topiramate combination. Each of these agents has been demonstrated to induce significant weight loss in patients who are overweight or have obesity.

Lorcaserin. Lorcaserin is a selective agonist of the 5-HT$_{2c}$ serotonin receptor. At clinically effective doses, lorcaserin does not activate the 5-HT$_{2B}$ receptor, which appears to be the receptor primarily responsible for the cardiac valvular disease associated with fenfluramine. Recent large, phase 3 trials of lorcaserin revealed no valvulopathy resulting from the use of this agent. These trials demonstrated an average weight loss of 5.8% of the subject's body mass, as opposed to 2.5% for those taking placebo.[34] However, the FDA panel voted against approving this drug in September 2010, stating that the benefits were too limited in the face of the risks associated with taking the drug. At the time of this writing, Arena pharmaceutical is still in discussion with the FDA for approval of this drug, and we should soon know the outcome.

Naltrexone-bupropion (Contrave). Naltrexone is an opioid receptor antagonist that has been used as an adjunctive therapy for the treatment of substance abuse and addic-

tion.[35] Bupropion has been shown to have modest but significant weight loss promoting effects. The combination of naltrexone and bupropion has recently been examined in a large phase 3 trial for the treatment of obesity.[36] These two agents are reported to synergistically block β-endorphin–mediated inhibition of pro-opiomelanocortin neurons, leading to increased hypothalamic anorexigenic neuronal activity. Each on its own has been shown to reduce appetite and body weight in humans.[37] The combination drug of the two, called Contrave, may prove to be an attractive option for patients who are resistant to other agents. This drug has not been approved by FDA because of a deficiency related to cardiovascular safety. Orexigen pharmaceutical plans to conduct a randomized, double-blind, placebo-controlled cardiovascular outcomes trial to demonstrate that Contrave does not unacceptably increase the risk of major adverse cardiovascular events.

Phentermine-topiramate (Qnexa). Several clinicians have noted weight loss effects with topiramate. It was also noted that the combination of phentermine and topiramate can generate substantial weight loss in at least a subset of patients who exhibit little weight loss when treated with phentermine alone. This observation led to the development of fixed-dose combinations of phentermine and topiramate. The phase III EQUATE trial evaluated Qnexa vs. placebo in 756 obese subjects over 28 weeks. Patients taking full-dose and mid-dose Qnexa achieved an average weight loss of 9.2% and 8.5% respectively, compared with 1.7% reported for the placebo group.[38] This drug recently received 20-2 votes by an FDA panel. The FDA is expected to decide whether to approve Qnexa by April 17, 2012.

Selected diabetic medications (metformin, exenatide, pramlintide)

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 (1-2%). Glucagon-like peptide-1 (GLP-1) is believed to act with other postprandial gastrointestinal signals such as gastric distention to promote satiety, delay gastric emptying, and reduce food intake,[39] and liraglutide has been shown to have the same effect.[40] Astrup et al investigated liraglutide's effect on weight compared with that of open-label orlistat in a double-blind, placebo-controlled 20-week trial that consisted of 564 European subjects without diabetes. Subjects treated with all doses of liraglutide lost more weight than those taking placebo ($p < 0.05$), and those treated with 2.4 or 3.0 mg of liraglutide lost more weight than those taking orlistat ($p < 0.05$).[41] 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%). Recently, an extended-release formulation of exenatide with the brand name of Bydureon (Amylin Pharmaceuticals, San Diego, CA) has also been approved by the FDA. This is an injectable form that is given once a week. Amylin, a peptide co-secreted with insulin from pancreatic β cells, inhibits gastric emptying and glucagon secretion and promotes satiety. 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 one-year study of pramlintide in patients with type 2 diabetes, patients lost 0.4 kg compared with a 0.8-kg weight gain in the placebo group.[42]

Very-low-calorie diet program

Very-low-calorie diets (VLCDs) are defined as diets limiting energy intake to 1.88-3.35 MJ (450-800 kcal) per day while providing at least 50 g of high-quality protein and amino acids, essential fatty acids, and daily requirements of trace elements, vitamins, and minerals. They are recommended only in the obese (BMI 30 kg/m^2) or in individuals with BMIs >27 kg/m^2 plus one or more comorbidities. After initiation of a VLCD, hyperglycemia decreases within 4-10 days, even before significant weight loss has occurred.[43,44] Modern VLCD programs are extremely safe, with no increased rate of cardiac arrhythmias[45] or electrolyte abnormalities.[46] It is still important that these programs be supervised by a medical doctor trained in the management of obese patients.

Weight loss surgery

Surgical options are appropriate in patients with high BMIs (>35 kg/m^2) and type 2 diabetes who have not been able to lose significant amounts of weight through lifestyle interventions alone or lifestyle interventions combined with weight loss medications. In obese patients who also have type 2 diabetes, bariatric surgery results in remission (defined as normoglycemic control without the need for diabetic medications) in more than three fourths of cases, with higher rates with the Roux-en-Y gastric bypass procedure than with the laparoscopic adjustable gastric banding procedure.[47] After bariatric surgery, patients lose more weight than with traditional weight loss methods—up to 25% of their total body weight. Furthermore, of those with type 2 diabetes, 87% achieve at least better glucose control and need fewer antidiabetic medications, and an average of 78% achieve normal glycemic control without taking *any* antidiabetic medications.[48]

Weight loss surgeries can be classified as two major types: (1) Gastric restrictive procedures and (2) intestinal bypass procedures. The classification was initially based on the presumed mechanism of weight loss.

Gastric restrictive procedures (laparoscopic adjustable gastric banding, sleeve gastrectomy, vertical gastroplasty) limit gastric volume and, hence, restrict the intake of calories by inducing satiety. After the procedure, patients lose approximately 10-20% of their total body weight. Furthermore, multiple studies, including a randomized, controlled

trial[49] have shown remission of type 2 diabetes with laparoscopic adjustable gastric banding but not with conventional medical therapy. The effect is primarily mediated by weight loss and improved insulin sensitivity, both of which occur several months after surgery. Of note, however: in this trial, all patients had diabetes of short duration (<2 years).

Intestinal bypass procedures (Roux-en-Y gastric bypass, biliopancreatic diversion) also restrict caloric intake, similar to gastric banding and vertical gastroplasty. Because the small intestine is shortened in intestinal bypass procedures, there is an added component of malabsorption of fat and nutrients. After the procedure, more patients experience remission of type 2 diabetes (82-99%) than after gastric restrictive operations, even patients with longer duration of disease, including those treated with insulin.[29]

Conclusions

Type 2 diabetes is a progressive disease that can become more difficult to treat with time. Obesity leads to increased inflammation and insulin resistance. Weight loss can help reduce the insulin resistance and improve hyperglycemia. Health care providers should evaluate for obesity and weight gain in diabetic patients and offer lifestyle modification treatment, including behavior modification, diet, and physical activity therapies. When these treatments are not enough, weight loss medication and/or bariatric surgery therapies should be offered in conjunction with lifestyle modification treatment.

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