

Treatment for Obese Diabetics

Introduction

Excess weight and obesity have reached epidemic proportions in the United States. One-third of US adults and 16% of children are obese with a body mass index (BMI) of 30 or more.¹ Two out of three adults are overweight or obese.² Obesity dramatically increases the risk of type 2 diabetes, hypertension, dyslipidemia, stroke, osteoarthritis, myocardial infarction, certain cancers, sleep apnea, and infertility in women.¹⁻⁴ Excess mortality is associated with BMI of 35 or more and waist to hip ratios greater than 0.9.⁵

Cardiometabolic syndrome or metabolic syndrome is a constellation of risk factors that increase the risk of atherosclerotic cardiovascular disease, stroke, and sudden death.^{6, 7} The criteria defining cardiometabolic syndrome have evolved with input from numerous expert panels since 1998 when the World Health Organization (WHO) defined metabolic syndrome. The syndrome is generally recognized as including a measure of excess weight (BMI, waist circumference, or waist to hip ratio), dyslipidemia, and elevated blood pressure. The WHO, European Group for the Study of Insulin Resistance, National Cholesterol Education Program Adult Treatment Panel III, and the American Association of Clinical Endocrinologists definitions also include a measure of insulin resistance or prediabetes.⁶ Each of the definitions of metabolic syndrome sets different cut points for its diagnosis potentially leading to confusion for its use as a clinical measure, however, it has utility in identifying persons at elevated risk for long-term morbidity and early mortality including sudden death.⁷

Persons with prediabetes are at risk for cardiovascular disease, retinopathy, nephropathy, and stroke.^{8, 9} Once diabetes emerges among people with metabolic syndrome cardiovascular risk is enhanced.⁶ Persons with diabetes and only one of the other cardiometabolic syndrome risk factor are at elevated risk for cardiovascular disease.¹⁰

Environment and Genetics

All definitions of cardiometabolic syndrome include measures of excess weight. The prevalence of obesity among adults more than doubled from 15% in the late 1970s to 32% in 2004.¹¹ The increase in prevalence of obesity is due to both environment and genetics.¹² Easy access to energy dense foods high in fats and sugars and increasing use of automated transport have lead to greater caloric intake and lower expenditure. In addition, it is recognized that there are genetic components to weight gain. The overall heritability of obesity is estimated to be from 40% to 70%.¹³ While numerous genetic candidates have been identified as contributing to a propensity for weight gain,¹⁴ the fat mass and obesity-associated (FTO) and melanocortin 4 receptor (MC4R) genes are recognized as impacting weight.¹⁵⁻¹⁷ The FTO gene has been associated with a 1.67-fold increased risk for obesity,¹⁵ while, on the other hand, the MC4R gene conveys hypothalamic signals that suppress food intake and increase energy expenditure.¹⁴ Mutations to the MC4R gene are established causes of obesity.¹³

Comorbidities

The prevalence of obesity and its association with type 2 diabetes, hypertension, and dyslipidemia highlight the need for a global approach for management of excess weight and comorbid disease. Excess weight has additional secondary impacts on hormone balance, osteoarthritis, and lung disease. Obesity is recognized as affecting fertility in both women and men.³ In women, obesity results in menses irregularities, chronic oligo-anovulation, and miscarriage. In men, obesity can alter the hormonal milieu, reduce spermatogenesis, and lead to erectile dysfunction. Increasing body weight in men leads to reduced total and free testosterone blood concentrations while increasing estrogen production. In addition, men with type 2 diabetes have significantly lower testosterone levels than men without diabetes.⁴ Testosterone replacement therapy may be a viable option although prostate cancer and male breast cancer are contraindications.⁴ Obesity is recognized as a contributor to

osteoarthritis (OA) in weight-bearing joints, particularly the knees.¹⁸⁻²⁰ Risk of OA increases with increasing BMI.^{18, 19} Obesity is also associated with asthma, obstructive sleep apnea, pulmonary embolic disease, and aspiration pneumonia.²¹

Treatment

Current weight-loss practices may entail the use of caloric restriction, exercise, weight-loss medication, or some combination of these methods. The National Heart, Lung, and Blood Institute (NHLBI)^{14, 22} recommends the use of diet and physical activity for weight loss for persons with BMI above 25. For persons of BMI of 30 or more or BMI above 27 with weight-related morbidity where diet and exercise have not been successful, the NHLBI recommends the use of weight-loss medication. The NHLBI and the American Association of Clinical Endocrinologists, the Obesity Society, and Society for Bariatric Surgery (AACE/OS/SBS) recommend bariatric surgery for persons with BMI of 40 or greater and for persons with BMI of 35 or greater who have significant comorbidities such as cardiovascular disease or type 2 diabetes.^{23, 24}

NHLBI Weight-Loss Guidelines^{22, 24}

Method	BMI				
	> 25 – 26.9	27 – 29.9	30 – 34.9	35 – 39.9	> 40
Diet, exercise, behavioral therapy or a combination	√	√	√	√	√
Weight-loss medication		Patients with weight-related morbidity	√	√	√
Bariatric surgery				Patients with weight-related morbidity	√

Diet and Exercise

Increased physical activity without a reduction in caloric intake results in only modest weight reduction.²⁴ The combination of caloric restriction and exercise can reduce abdominal adipose tissue, improve insulin resistance, and tends to result in greater weight reduction. Resistance training may be particularly helpful in modifying body composition (fat mass versus lean mass). Caloric restriction and aerobic exercise increase HDL cholesterol and reduce triglycerides and blood pressure.

Meal replacement products (MRP) may be utilized to manage total caloric intake and help improve body composition and reduce blood pressure.²⁴ MRP can result in weight loss of 9% to 10% of total body weight in six to 12 months and 6% to 8% over the long term (from one to five years).²⁵ Improvements in glucose control for diabetic patients can be achieved within days and last as long as weight loss is maintained plus improvements are seen in blood pressure and serum cholesterol and triglycerides.²⁵ Solid meal replacement products appear to be more effective in reducing hunger than liquid products.^{26, 27}

Weight-loss Medications

Weight-loss medications typically result in weight loss of less than 5 kg.²⁸ There may be patients for whom surgery is not recommended, however, and primary care providers may want to utilize weight loss medication, in particular where advantages may be derived from improvements in cardiovascular indices and insulin

resistance.²⁹ While weight loss from these medications tends to be limited, clinical impacts can be significant.³⁰ A weight loss of only 5% to 10% may be sufficient to improve blood pressure, fasting glucose, triglycerides, and HDL cholesterol.²⁴ Weight loss medications should be used in conjunction with diet and exercise programs to achieve these goals.

Because obesity is a chronic disease and weight gain recurs when medication use ceases, use of weight loss medications should be initiated as a long-term treatment strategy.³¹ Currently, there are two drugs approved for long-term use by the FDA: orlistat and sibutramine. Rimonabant has not been approved by the FDA and was recently pulled from the European market due to issues with mood disorders.⁴ Orlistat³² is a lipase inhibitor and limits intestinal digestion of fat. Orlistat can reduce diabetes incidence, improves cholesterol levels, blood pressure, and glycemic control. Orlistat, however, can cause oily stools and fecal urgency. About 5% of patients discontinue its use due to gastrointestinal side effects. Orlistat can reduce the absorption of fat-soluble vitamins²² and a vitamin supplement may be required when taking orlistat. The Food and Drug Administration has approved a 60 mg, over-the-counter form of orlistat. Sibutramine³² is a selective inhibitor of the reuptake of norepinephrine, serotonin, and dopamine. It reduces food consumption and the percentage of fat eaten. Sibutramine can improve HDL cholesterol and triglyceride levels but may increase blood pressure and heart rate. Sibutramine can cause insomnia, nausea, and constipation.

New and Emerging Weight-loss Medications

With a paucity of long-term medications available for weight loss, there is an effort to develop additional pharmacotherapy options. Currently, there are over 50 medications undergoing testing in clinical trials for efficacy and safety.³³

Classes of Weight-loss Medications Under Investigation³²

Class/Hormone	Mode of Action
Leptin	Cytokine acting on the gp130 family of cytokine receptors; absence of leptin causes massive overweight in humans
Neuropeptide Y Receptor Antagonists	Block neuropeptide Y, which stimulates food intake, inhibits energy expenditure, and increases body weight
Serotonin 2C Receptor Agonists	Block 5-HT _{2C} receptors and suppress food intake
Peptide YY ₃₋₃₆	A GI hormone secreted in proportion to the caloric contents of a meal that reduces appetite
Oxyntomodulin	GI peptide released in response to food that suppresses appetite
Pancreatic Lipase Inhibitor	Prevents absorption of fat from the GI tract
Cholecystokinin	Peptide hormone of the GI tract that acts as a hunger suppressant
Melanin-Concentrating Hormone Receptor-1 Antagonists	Reduce food intake by decreasing meal size
Histamine-3 Receptor Antagonists	Reduce food intake
Ghrelin Antagonists	Suppression of food intake
Angiogenesis Antagonists and Fat Cell Antibodies	Inhibit blood supply to fat cells

Treating Obese Patients with Diabetes

Diabetic medications have the potential to increase weight.³⁴ Medications that are weight neutral or induce weight loss should be considered for overweight diabetic patients.

Diabetic Medications, Impact on Weight, and Side Effects³⁴

Diabetic Medication or Class	Impact on Weight	Side Effects
Metformin	Neutral or small reduction	GI side effects, rarely lactic acidosis
Acarbose	Neutral or small reduction	Poorly tolerated due to frequency of GI effects
Sulphonylureas	Gain	Hypoglycemia
Glinides	Gain	Hypoglycemia ³⁵
Thiazolidinediones	Gain	Fluid retention
Insulin	Gain	Hypoglycemia
Incretin-based Therapies GLP-1 Mimetics DPP-4 Inhibitors	Loss Neutral	Nausea, vomiting; diarrhea Free of GI effects, low risk of hypoglycemia

Bariatric Surgery

For the majority of obese patients, bariatric surgery results in significant, long-term weight loss.³⁶ Gastric banding results in a loss of 45 to 72 pounds for up to six years of follow up, while Roux-en-y gastric bypass results in 53 to 77 pounds lost.³⁷ Type 2 diabetes is resolved in 80% to 100% of patients. A meta analysis of 129 studies revealed that adjustable gastric banding can resolve hypertension in 43% or more of patients.³⁸ Recently, a randomized trial³⁹ revealed that over a two-year observational period laparoscopic adjustable gastric banding for persons with BMI between 30 and 40 was significantly more likely than diet and exercise to eliminate type 2 diabetes, reduce weight, and improve dyslipidemia. In this study, diabetes was resolved in 73% of patients undergoing gastric banding. Nutritional deficiencies can occur with either gastric banding or bypass surgery, but are more common with gastric bypass.³⁷

Summary

Obesity and excess weight are at epidemic proportions in the US population. Cardiometabolic syndrome, a measure of excess weight, dyslipidemia, and hypertension, places patients at increase risk for cardiovascular disease. Once diabetes is manifest, risk of a cardiovascular event is increased. Early recognition of factors increasing the risk of cardiovascular disease and prompt treatment will lessen morbidity and early death among obese diabetics. Learning objectives 1 through 5 will heighten clinicians' awareness of increased risk and allow them to actively lessen risk of cardiovascular disease and comorbid conditions, decrease likelihood of aggravating weight gain, and reduce life threatening events in obese diabetics.

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