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## MANAGEMENT OF OBESITY IN THE PREVENTION OF CARDIOVASCULAR DISEASE

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### Introduction

The prevalence of obesity is increasing in the United States and many other countries, and has now passed smoking as the most preventable cause of morbidity and mortality<sup>1</sup>. Obesity is an excess of adipose tissue that results from a mixture of genetic predisposition, environmental influences (e.g., sedentary lifestyle), and behavioral components (e.g., food as a reward), and it is a chronic, relapsing condition. The rapid increase in obesity prevalence is, however, not due to genetic changes but rather is a societal mismatch between physiology and environment, where food is abundant and exercise is unnecessary. The definition of excess adipose tissue, for the purpose of correlating this to disease outcomes, is through body mass index (BMI), which is calculated as weight (kg)/height (m<sup>2</sup>). Overweight is a BMI of 25–29.9 kg/m<sup>2</sup>, and obesity is a BMI  $\geq 30$  kg/m<sup>2</sup>. There is evidence that all-cause mortality is higher in obese people, primarily due to increased cardiovascular disease (CVD) mortality and increased obesity related cancer (colon, breast, uterine, ovarian, renal, and pancreatic) mortality<sup>2</sup>.

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### Co-Morbidities of Obesity

There are many other disease consequences of overweight and obesity, and the severity of many are related to higher baseline BMI. In general, most cardiovascular risk factors increase linearly with BMI, such as hypertension, low levels of high-density lipoprotein (HDL) cholesterol, metabolic syndrome, and type 2 diabetes.

Other important consequences of obesity include sleep apnea, polycystic ovarian syndrome, cholelithiasis, non-alcoholic steatohepatitis, and weight-bearing osteoarthritis. The incidence of type 2 diabetes increases at least 3-fold in men and 5-fold in women with obesity and specifically with the presence of central adiposity. Abdominal fat accumulation, as measured by waist circumference, is an important determinant of many metabolic disturbances that are clinically referred to as the metabolic syndrome. The defining cut points for elevated waist circumference (WC) are  $>102$  cm (men) and  $>88$  cm (women) in the United States, and  $>90$  cm (men) and  $>80$  cm (women) of Asian descent. Both BMI and metabolic syndrome are equally predictive of CVD,

and certain triad components of the metabolic syndrome, such as blood pressure/WC/glucose and blood pressure/low HDL/high triglycerides, bring at least a 2-fold higher risk of CVD events.<sup>3,4</sup>

The close relationship between the presence of central adiposity and the individual factors of the metabolic syndrome has suggested that adipose tissue in the abdominal area may play a significant role in producing the metabolic disturbances. In many people, enlargement of adipose cells leads to a proinflammatory situation such that these cells reduce their production of adiponectin and increase the secretion of cytokines and chemokines such as interleukin-6 and macrophage chemotactic protein-1 (MCP-1).<sup>5</sup> The abdominal adipose tissue in this situation has a characteristic microscopic increase in local macrophage accumulation, as well as resistance to insulin action, that leads to a lipolytic state. The resultant increase in free fatty acid release provides ample hepatic substrate to increase the storage of triglyceride in the liver, leading to steatosis. Recent work has also linked low HDL-C and potential reduced reverse cholesterol transport to the increased accumula-

tion of macrophages in dysfunctional visceral adipose tissue.<sup>6</sup>

Increased hepatic fat accumulation (steatosis) leads to further local insulin resistance such that hepatic gluconeogenesis is not suppressed, which can produce impaired glucose tolerance. Reduced adipose tissue production of adiponectin also contributes to hepatic insulin resistance. The combination of hepatic insulin resistance and increased hepatic production of triglycerides — which subsequently leads to skeletal muscle triglyceride accumulation and reduced myocyte glucose disposal — may be the reason many patients with abdominal obesity can progress to diabetes. With regard to myocyte triglyceride accumulation, particularly in cardiac muscle, there is evidence that diastolic dysfunction in type 2 diabetes is related to the fat content as measured by magnetic resonance (MR) spectroscopy. Importantly, weight loss in these subjects reduced myocardial triglyceride content and improved diastolic function.<sup>7</sup> However, not all obese patients have metabolic disturbances or evidence of insulin resistance. In one study using MRI to measure subcutaneous and visceral adiposity, as well as using MR spectroscopy to assess hepatic and skeletal muscle fat content, the researchers found that insulin resistance in similarly obese patients was dependant on the total amount of fat in the liver and muscle despite having similar quantities of visceral fat.<sup>8</sup> They concluded that just measuring BMI and visceral fat did not predict who would have insulin resistance. In an analysis of NHANES participants between 1999 and 2004, researchers found >2 metabolic abnormalities in 51% of subjects with a BMI of 25–29.9 and 32% in those with BMI >30. In contrast, 35% of women and 29% of men with a BMI >30 had a normal metabolic profile and they were termed “metabolically benign” obese.<sup>9</sup> Although a substantial number of obese patients may not have the metabolic abnormalities that we would relate to increased CVD and/or diabetes risk, the presence of obesity alone still predicts a higher all-cause mortality, as shown in another 9-year follow-up of NHANES participants.<sup>10</sup>

## Weight Reduction Strategies

Weight loss induced by caloric restriction has improved most of the metabolic abnormalities induced by insulin resistance.<sup>11</sup> As a result, modest reductions in weight, such as 5–10% of baseline weight, has been shown to reduce fasting glucose, hemoglobin A1C, blood pressure, and serum triglycerides as well as increase HDL-C. Weight loss also improves the severity of sleep apnea, the pain of weight-bearing joint osteoarthritis, and fertility in women with polycystic ovarian

syndrome. The National Institute of Health has recommended treatment to reduce weight by at least 5–10% from baseline in people with a BMI of 27–29.9 (or high WC) and >2 risk factors, and in all people with BMI >30. The treatment recommended to reduce weight has always been based on lifestyle modification: caloric restriction by at least 500 Kcal/day, increase in physical activity (30 minutes/day of moderate intensity, at least 5 days a week), and modification of behavioral patterns that have permitted overeating and limited activity. Medications can be used to assist with the implementation of lifestyle changes, and the FDA has approved phentermine and diethylpropion for short-term use (<12 weeks) and bupropion, sibutramine, and orlistat for longer use (up to 1 year). Although it has been known that blood pressure and pulse may be increased in some people given sibutramine, the results of a long-term outcomes trial with sibutramine suggested there may be more cardiovascular disease harm than benefit in some high-risk people. The FDA has recently added this warning to the sibutramine label, and as a result, this action diminishes the long-term usefulness of this drug in weight management.

There are myriad diet plans that can be used to initiate a weight-loss program. Although all are caloric-reduced, these plans can be grouped by how they arrange the dietary components: low-fat (<30% of total calories) and high carbohydrate (>50% of calories), high protein (>30% of calories) and low carbohydrate, and an equal caloric distribution between fat, protein, and carbohydrate. Regardless of diet composition, clinical studies show the average weight loss over 12 months is generally the same.<sup>12</sup> High protein/low carbohydrate diets may have greater adherence and weight loss in the short term (12 weeks) but not in the long term compared to other compositions. Importantly, diet composition, regardless of whether it is used for weight control or not, has an important relationship to CVD risk. Protective dietary factors include consumption of vegetables, nuts, monounsaturated fats (Mediterranean-type diet), and low glycemic index foods.<sup>13, 14</sup> Increased dietary intake of sugar has been associated with obesity, risk for type 2 diabetes, and CVD, and this is closely linked to the consumption of sugar-sweetened beverages.<sup>15</sup> An AHA Scientific Statement recently recommended limiting added sugar to a maximum of 150 Kcal/day. Interestingly, the adverse effect of food consumption that has a high glycemic index and glycemic load is greater for women than for men.

More rapid weight loss with hunger suppression can be achieved with a very low carbohydrate diet (VLCD, 800 cal/day) that focuses on protein content; however,

the ketosis and diuresis that occurs needs to be monitored in a multidisciplinary program with experienced healthcare professionals and a registered dietitian. Such a VLCD program is available at The Methodist Hospital, with participants having an average starting BMI of 40 and an average age of 48 years. Over 16 weeks, the average weight loss of all starters (by intention-to-treat analysis) is 34 pounds for women and 47 pounds for men, which is an approximate 15% (women) and 18% (men) loss from baseline. For those patients that completed at least 12 weeks, the loss of baseline weight was 23% for both men and women. Maintenance of weight loss is the most challenging and formidable stage for most people who have achieved reasonable success with a weight-reducing program, and recidivism is so common that only 5–10% are able to stay within 10 pounds after 1 to 2 years. In the Methodist program, where weekly group sessions and an online blog/chat room engage participants to practice healthy lifestyle changes, the average weight regain is only 5 pounds at 1 year.

Bariatric surgical options have become more widespread in the past decade as they have proven to have low perioperative mortality and very good long-term outcomes. The most commonly performed procedures are the laparoscopic gastric band, the Roux-en-Y gastric bypass, and most recently the vertical sleeve gastrectomy. The improvement in comorbidities such as hypertension, dyslipidemia, diabetes, and sleep apnea is highly significant, and average weight loss is good, with greater efficacy from the gastric bypass compared to the gastric band.<sup>16</sup> The greater initial weight loss with gastric bypass compared to banding is probably the result of both a restrictive intake of calories plus a moderate malabsorptive loss of calories, and the latter effect contributes to a more durable loss of weight. In general, the weight loss induced with surgery translates into a long-term (7–15 year) reduction in all-cause mortality.<sup>17, 18</sup>

Regardless of how weight is lost, an important component of weight maintenance, as well as the impact of BMI on cardiovascular and diabetes risk, is physical activity. Recent data from the Women's Health Study confirms that women who better maintained weight over a 13-year period averaged 60 minutes of moderate-intensity activity per day.<sup>19</sup> A debate has occurred over whether it is better to have a lower BMI or to be more physically fit. There is clearly an inverse relationship between fitness and morbidity/mortality; however, the question is whether just increasing fitness in obese people could be a more efficient approach than getting them to lose/maintain weight. Data does exist to support this, suggesting that low cardiorespiratory fit-

ness is a greater risk for CVD death than obesity, and that increased fitness diminishes the impact of obesity on mortality.<sup>20</sup> To underscore the impact of physical inactivity on cardiovascular disease, a recent study of television viewing time showed a direct relationship to cardiovascular and all-cause mortality.<sup>21</sup> The current recommendation for physical activity in all adults by the U.S. Preventative Task Force is for at least 30 minutes of moderate-intensity exercise at least 5 days/week (minimum 150 minutes/week), and this should be the minimum goal for all patients in maintenance after medical and surgical weight-loss programs.

Research continues in the pharmacologic treatments for obesity. There has been little progress with new drugs in the past decade, with the most recent medication, rimonabant, not receiving FDA approval. Targets for intervention are the central nervous system regulation of hunger/satiety and the gastrointestinal hormone signaling pathway. The redundancy of the hunger/satiety interplay is an evolutionary plan to deal with the thousands of years of food scarcity that humans encountered. The past hundred years of relative abundance of a food supply has not allowed a genetic change to accommodate.

Drugs that target hypothalamic areas have been studied, and they produce only modest weight loss partly because of alternative compensatory mechanisms that eventually override the initial effect. Gut hormones, such as GLP-1 agonists, seem to do fairly well because they delay gastric emptying, resulting in a mild to moderate sense of nausea. There are also central effects of GLP-1 that contribute to its durability on weight loss. There are currently several drug combinations in clinical phase III trials, such as naltrexone/bupropion, pramlintide/metreleptin, topiramate/phentermine, and zonisamide/bupropion. The preliminary results suggest good efficacy (at least 5–10% weight loss) and low adverse events. There is, however, no data concerning durability/safety beyond 1 year.

## Conclusion

Obesity is the most preventable cause of death in the country. Excess adipose tissue, especially visceral, contributes to increased risk for CVD and progression to type 2 diabetes. Weight loss of as little as 5–10%, through caloric restriction, reduces insulin resistance, improves glucose control, reduces blood pressure, and increases HDL-C in the near term and probably reduces mortality in the long term. Caloric restriction (>500 kcal/day) can be achieved by any reasonable diet plan to initiate weight reduction, and more extensive caloric

reduction (such as a VLCD) can produce substantial weight loss in a supervised program. Bariatric surgery also results in similar percent weight reduction as a VLCD, and the long-term outcomes are outstanding. Pharmacologic treatment for obesity is challenging, and short-term therapies may prove to be safe and effective. However, long-term maintenance drug treatment may not be a reality for many years. Weight maintenance is a challenging endeavor that requires coaching from dietitians and behavior specialists to provide structure for patient compliance regarding meal planning and physical activity.

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