OBESITY AND CARDIOVASCULAR DISEASE: A BAD RELATIONSHIP THAT NEEDS TO CHANGE

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INTRODUCTION

Obesity is strongly associated with an increased risk of cardiovascular disease, and conventional wisdom reasons that reducing weight would favorably reduce that risk.1 An abundance of evidence associates excess adipose tissue, particularly in the visceral compartment, with insulin resistance, a risk for developing diabetes, increased blood pressure and lipoprotein disorders (low high-density lipoprotein, cholesterol and high triglycerides). There also is evidence that short-term weight loss can improve insulin sensitivity, reduce blood pressure and improve lipoprotein levels.[2] Unfortunately, there are no long-term randomized clinical trials that demonstrate a reduction in cardiovascular endpoints with sustained weight loss. An obvious explanation is the lack of effective methods to induce and sustain weight loss over many years in most people.

The complex biologic and genetic relationship of hunger and energy balance is finally receiving much-needed scientific attention, and new research is focusing on lifestyle habits, such as the composition of food intake and exercise, and drugs that modulate hunger/satiety and energy expenditure. Even so, the dramatic global rise in obesity threatens the progress thus far in reducing cardiovascular disease (CVD) risk factors. This article examines the epidemic of obesity, its effect on traditional CVD risk factors and the effect of weight loss on controlling CVD risk.

OBESITY AND CARDIOVASCULAR DISEASE

Observational studies have established chat the risk of total and cardiovascular mortality increases progressively as the body mass index (BMI) rises over 25 kg/m[1]. Over the past decade, che prevalence of obesity has increased to where more than 30% of U.S. adults have a BMI 30 kg/m[2].[3] The prevalence is influenced by age, gender and ethnicity, wich a graded increase as one ages and a higher prevalence in women and Hispanics.

Obesity influences numerous disease states chat impact longevi$_{ty}$ and quality of life, such as type 2 diabetes, hypertension, coronary heart disease (CHO), stroke, obstructive sleep apnea, nonalcoholic fatty liver disease, osteoarthritis and cancer. Recenc anal$_{ys}$is from the National Health and Nutrition Examination Survey (NHANES) I, II and III chat followed patients from 1971 to 1994 show chat Caucasian men and women at age 20 with a BMI >45 have 8-13 years of lose life compared to similar-aged subjects with a BMI of 24.4 Likewise, African-American men and women with a BMI >45 at age 20 have 5-20 years of lost life.

This increase in obesity prevalence has not escaped our children, and this alarming trend is threatening their life expectancy.5 The cause is probably not the result of genetic alcerations. Although generics play a major role in one's propensity for obesity, the change in lifestyle habits - larger portion sizes, readily available high-calorie foods, sedentary lifestyle - over the past few decades has been a major contribucor.6

The healch benefics of weight loss have been confined to various low-caloric diets that produced at least a 5-10% reduction in body weight, which in turn showed significant reductions in systolic and diastolic blood pressure, glucose, LDL cholesterol and triglycerides and increases in HDL cholesterol. A recent meta-analysis of clinical outcomes from bariacric surgery has confirmed che impressive improvement in obesity-related comorbidicies with substantial weight loss.7 With an average loss of 60% of excess weight following surgery, 77% of type 2 diabetics had normal glucoses, 70% of dyslipidemic patients improved, 62% of hypertensives had resolucion, and 86% of obstructive sleep apnea subjects resolved their symptoms. Although there have been no hypocaloric diet or anorectic drug randomized clinical trials performed to evaluate hard cardiovascular endpoints, it is presumed chat che improvement in surrogate cardiovascular risk factors (blood pressure, glucose control, lipoproteins) with short-term weight loss would translate to long-term benefits. With chis in mind, the National Heart Lung and Blood Institute (NHLBI) recommends that weight-loss treatment be offered co patients with a BMI 30 or between 27-29.9 with two or more risk factors for vascular disease, one of which can be high waist circumference.[8] The goal of a weight-loss treatment should be 10% of baseline weight within six months followed by a mainrenance program and further weight loss if feasible. The NIH classification of overweight and obese - with the risk for type 2 diabetes, hypertension and

cardiovascular disease associated with waist circumference - is shown in Table 1.

OBESITY AND INSULIN RESISTANCE

As rhe prevalence of obesity has risen over the last decade, so too has the incidence of cype 2 diabetes. The vast majority of these cases are insulin resistant, meaning that the liver, skeletal muscle and adipose tissue are less responsive to insulin-medicated actions such as glucose uptake and lipogenesis. Although the exact cause of insulin resistance is not known, adipose tissue, particularly in the visceral location, is thought to play a permissive role. Adipocytes are known to secrete many products that can negatively affect insulin action - products such as nonesterified faery acids (NEFA), rumor necrosis factor (TNF-A), resistin, inrerleukin-6e - and chey fail co release a beneficial hormone, adiponeccin.[9] The compensatory hyperinsulinemia of insulin resistance, combined wirh increased free faery acids, leads to hepatic sreacosis and hepatic overproduction of triglycerides as well as increased renal sodium absorption chat can result in hypertension. The clustering of these clinical findings has been termed che "metabolic syndrome" and has been defined by several consensus organizations. The National Cholesterol Education Program Adule Treatment Panel (ATP) III requires three out of five for a diagnosis of metabolic syndrome (Table 2).10 To highlight the importance of abdominal obesicy, the International Diabetes Federation now uses increased waist circumference plus two of several other criteria to define metabolic syndrome.11 At least 25% of rhe U.S. adult population meets the ATP III metabolic syndrome criteria, and chis increases with age and in certain ethnic groups.[12] Recent studies confirm chat individuals with or without CHO who have metabolic syndrome are at increased risk of cardiovascular disease.[13,14]

Risk for Type 2 Diabetes, Hypertension and CVD

	BMI	Obesity Class	Waist Circumference	
			Normal	High
Overweight	25.0-29.9		Increased	High
Obesity	30.0 -34.9	I	High	Very High
	35.0-39.9	I	Very High	Very High
Extreme	40	III	Extremely High	Extremely High

High waist circumference: men >40 inches; women >35 inches

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Table 1. Classification of overweight and obesity

ATP III Criteria for the Metabolic Syndrome; Diagnose with any 3 of the following:

Risk Factor	Defining Level
Abdominal Obesity (waist circumference)	
Men	> 102 cm (>40 inches)
Women	>88 cm (>35 inches)
Triglycerides	150mg/dl
HDL-C	
Men	<40 mg/dl
Women	<50 mg/dl
Blood Pressure	130/ 85 mm Hg
Fasting Glucose	110 mg/dl (> 100 mg/dl)

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Table 2. ATP III criteria for the metabolic syndrome

Research has shown chat people with mecabolic syndrome who lose weight (approximately 7% of baseline) and exercise regularly (at least 150 minutes/ week) reduce the progression of diabetes by41%.15

It appears clear that central or abdominal obesity is not only a culprit in causing insulin resistance bur chat reducing weight can reverse che components of metabolic syndrome.

THE EFFECTS OF WEIGHT LOSS

The Methodisc Hospital Wellness Services has provided a rapid weighc-loss program for patients with BMI ?.30 for the past decade. It uses a very low-calorie (VLCD, 800 calories), low-carbohydrate, liquid protein plan that results in consistent weight loss of 2-5 pounds/week. Research conducted at the Methodist DeBakey Heart Center found this drastic caloric deficit diet ro improve the components of mecabolic syndrome within weeks, well before che patients lose substantial weight (Table 3).16 Accompanying the reduction in glucose, triglycerides and blood pressure was a lowering of plasma insulin and an improvement in the homeostatic model assessment of insulin resistance.

Based on previous assumptions that certain peptides are central to causing insulin resistance, we measured serum levels in metabolic syndrome patients on the liquid protein diet and found no reduction in TNF-A or NEFA nor an increase in adiponectin in the first four weeks (Table 4).17 These results suggest that while there are strong correlations between the peptides/hormones produced by adipocytes and insulin resistance, the observed improvement in glucose tolerance is not dependent on correcting chem nor on losing substantial fat mass. Continued **work** from **our** group on fat obtained from subjects before and after 4-6 weeks of VLCD participation has focused on the genetic expression of an array of important steps in energy metabolism. Preliminary results suggest a marked suppression of stearoyl coenzyme A desarurase 1 (SCD1), which would cause fat co be shunted from storage co energy metabolism.[18] It is possible that the early benefit on insulin sensitivity from marked caloric restriction is through suppression of SCD1 rather than increases in adiponectin, and that sustained improvement in metabolic syndrome components are from the increase in adiponectin that occurs with substantial weight loss.

CONCLUSION

As obesity approaches epidemic status in the United States, there are important implications on cardiovascular disease risk. The American Heart Association has addressed the issue in a conference symposium and states that weight loss and increased physical activity are the cornerstones for preventing obesity-related CHD risk factors.2 Recent studies with rapid weight-loss diets suggest that early improvements in insulin resistance and components of metabolic syndrome are mediated through mechanisms that regulate energy metabolism, and that long-term maintenance of insulin sensitivity is probably controlled by reduced visceral fat and improved adipose tissue function through release of adiponectin.

Variable	Initial	14 Weeks	P value
Weight	261	244 6.5%	< 0.001
BMI	40.7	38.2	< 0.001
Systolic BP	140 mm Hg	129 mm Hg	< 0.001
Diastolic BP	85 mm Hg	75mm Hg	< 0.001
Glucose	115	98 15%	< 0.001
Triglycerides	232	137 40%	< 0.001
Cholesterol	208	171 18%	< 0.001

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Table 3. Weight loss and the metabolic syndrome at 4 weeks

Variable	Before	After	Pvalue
BMI	39	36	< 0.001
Weight	257	239	< 0.001
SBP	135	129	0.01
DBP	85	80	< 0.001
Glucose	108	92	0.01
TG	280	127	< 0.001
HDL-C	44	41	< 0.001
LDL-C	118	98	0.001
NEFA	0.5	0.6	NS
hs-CRP	5.0	4.3	0.02
Insulin	168	59	< 0.001
HOMA-IA	7.7	2.3	< 0.001
Leptin	2964	1727	< 0.001
Adiponectin	7.5	71	NS
TNF-a	3.3	3.3	NS

Table 4. VLCD effects in metabolic syndrome at 4 weeks

REFERENCES

1. *Sowers JR. Obesity as a cardiovascular risk factor. Am J Med. 2003;115(Suppl BA): 537-41.*
2. *Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, et al. Clinical implications of obesity with specific focus on cardiovascular disease: A statement for professionals from the American Heart Association Council on Nutrition, Physical activity and Metabolism. Circulation. 2004;110:2952-2967.*
3. *Hedley AA, Ogden CL,johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents and adults, 1999-2002. JAMA. 2004:291:2847-2850.*
4. *Fontaine KR, &dden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity.JAMA. 2003:289:187-193.*
5. *Olsharsky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. 2005;352:1138-1145.*
6. *Manson JE, Skerrett PJ, Greenland P,*

Van Itallie TB. The eJcalating pandemics of obesity and sedentary lifestyle. Arch Intern Med. 2004; 164:249-258.

1 Buchwald H, Avido Y Braunwald E, Jensen MD, Pories W. Fahrbach K, et al. Bariatric surgery; A systematic review and meta-analysis. JAMA. 2004;292:1724-1737.

8. National Institutes of Health. Clinical guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults-The Evidence Report. Obes Res. 1998 Sept; 6 (Suppl 2):S51-209.

9. Ruan H, Lodish HF. Regulation of insulin sensitivity by adipose tissue-derived hormones and inflammatory fytokines. Curr Opin Lipidol. 2004 jun; 15(3):297-302.

IO. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive mmmary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285:2486-2497.

11. International Diabetes Federation [homepage on the Internet]. Belgium; c2003 {updated 2005 Apr 14; accessed 2005 Jul]. The IDF consensus worldwide definition of the metabolic syndrome. Available from www. i d forg

12. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-359.

13. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomi/ehto J et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA. 2002,288:2709-2716.

14. Levantesi G, Macchia A, Marfisi RM, Franzosi MG, Maggioni AP. Nicolosi GL, et al. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. J Am Coll Cardiol. 2005; 46(2):277-283.

15. Orchard TJ, Temprosa M. Goldberg R, Hajfoer S, Ratner R, Marcovina S, Fowler S, for the Diabetes Prevention Program Research Group (2005). The effect of metformin and intense lifestyle intervention on the metabolic syndrome: The Diabetes Prevention Program Randomized Trial. Ann Intern Med. 2005;142:611-619.

16. Case CC, *Jones PH, Nelson K, O'Brian Smith E, Ballantyne CM. Impact of weight loss on the metabolic syndrome. Diab Obesity Metab. 2002;4:407-414.*

17. Xydakis AM, Case CC, *Jones PH, Hoogeveen RC. Liu M-Y, Smith EO, et al. Adiponecti11, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight loss through caloric restriction. J Clin Endocrinol Metab. 2004;89(6):2697-2703.*

18. Cohen P. Friedman JM. Leptin and the control of metabolism: role for stearoyl-CoA desaturase 1 (SCD-1}. J Nutr. 2004; 134(Suppl):S2455-2463.