The Relationship Among Risk Factor Clustering, Abdominal Obesity, and Residual Risk for Cardiovascular Events

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Statins, angiotensin-converting enzyme inhibitors, and combination therapies have been shown to reduce the cardiovascular event rate in susceptible individuals, albeit with remaining significant residual risk. Some of the sources of residual risk, such as genetics and epigenetic phenomena, are not easily modifiable. Still, the risk imposed by these factors may be lowered by implementation of dietary, behavioral, and pharmacologic interventions. Abdominal obesity has emerged as one element in the cluster of factors linked to increased propensity for cardiovascular disease and type 2 diabetes. It is a potential therapeutic target to reduce residual cardiometabolic risk. Waist circumference has been shown to be a strong correlate of abdominal obesity, and measurement is a useful tool for the assessment of cardiometabolic risk.
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Key words: Cardiovascular risk • Abdominal obesity • Waist circumference • Type 2 diabetes

Cardiovascular disease is the leading cause of mortality in the world.[1] In the United States, despite reductions in cardiovascular-related mortality over the last quarter century, it remains the leading cause of death.[2] Primary prevention focuses on population approaches that emphasize a healthy lifestyle and identification of high-risk individuals who qualify for pharmacologic therapy. Secondary prevention emphasizes management with lifestyle modifications and pharmacologic therapy. Pharmacotherapy with

statins, angiotensin-converting enzyme (ACE) inhibitors, or a combination of agents has been shown in randomized clinical trials to reduce risk for cardiovascular events in the primary and secondary prevention of cardiovascular disease. However, even when treatment goals are achieved, significant residual risk remains. This observation suggests that the current treatment approaches may be too narrow to have a significant effect on cardiovascular risk reduction, and that there may be a need to consider other intervention targets. This review focuses on the role of abdominal obesity as a key element in the cluster of risk factors linked to increased risk for cardiovascular disease and type 2 diabetes, and proposes that abdominal obesity is an appropriate target for reduction of residual risk.

Progress in Cardiovascular Disease Prevention

Our current understanding of modifiable and non-modifiable predictors of increased risk for cardiovascular disease is exemplified in the INTERHEART study, a case-control examination in 52 countries that evaluated 15,152 cases of acute myocardial infarction (MI) compared with 14,820 age- and sex-matched controls.[3] The study determined that an abnormal ratio of apolipoprotein (apo) B to apoA-1 and smoking accounted for about 67% of the population attributable risk of acute MI. Seven additional risk factors—diabetes, hypertension, psychosocial stress, waist-to-hip ratio, insufficient fruit and vegetable consumption, inadequate exercise, and alcohol consumption (listed in order of the strength of their individual contribution)—increased the population attributable risk by about 27%. Maintaining a healthy weight, abstaining from smoking, eating a healthy diet, consuming only a moderate amount of alcohol, partaking in regular exercise, and living a stress-free life could prevent much of the risk for MI (90% according to the INTERHEART study and 84% according to the Nurses' Health Study[4]). However, only a small percentage of the population in the United States follows these guidelines; in the Nurses' Health Study only 3% of subjects did.

Taken together, the findings in the INTERHEART study and the Nurses' Health Study suggest that it is important to incorporate lifestyle management into an effective treatment plan. However, because more than 60% of United States adults are overweight,[5] it is inconceivable that the population can be shifted to a healthy weight; therefore, the focus of intervention strategies must be on improving risk within the confines of the current environment. In addition to identification of high-risk individuals, a current mainstay of cardiovascular risk reduction is the use of statins to lower elevated low-density lipoprotein (LDL) levels and raise abnormally low high-density lipoprotein (HDL) levels.

Statins and Cardiovascular Risk Reduction

Primary prevention studies using pharmacotherapy interventions that target lipids have consistently shown reduction in risk for cardiovascular events and, in some cases, for cardiovascular mortality. The West of Scotland Coronary Prevention study was the first to demonstrate that use of pravastatin reduced rates of cardiovascular disease and overall mortality, as well as of nonfatal MI and coronary interventions.[6] Additional studies using lovastatin[7] and atorvastatin[8] demonstrated the value of using statins for the primary prevention of cardiovascular events.

Similarly, secondary prevention studies have demonstrated that statins can reduce cardiovascular events in patients who have diabetes or established cardiovascular disease. In the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study, simvastatin use was associated with a reduction in coronary mortality, MI, stroke, and revascularization procedures.[9] In addition, recent meta-analyses have provided evidence that lipid-lowering drug treatment with statins significantly reduces cardiovascular risk in patients who are diabetic, nondiabetic, hypertensive, normotensive, or smokers, although the benefit seems greater in patients with diabetes than without.[10,11]

A recent trend has been to attempt to lower LDL levels to even more stringent levels. The Treating to New Targets (TNT) trial randomized 10,001 patients with stable coronary heart disease to atorvastatin 10 mg or 80 mg with LDL cholesterol goals of 100 mg/dL (2.6 mmol/L) or 75 mg/dL (1.9 mmol/L), respectively.[12] At a median follow-up of 4.9 years, mean LDL cholesterol levels were 77 mg/dL for the high dose of atorvastatin compared with 101 mg/dL for the low dose. A primary event occurred in 8.7% of those treated with the high dose compared with 10.9% of those on the low dose.

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However, these studies also demonstrate that statin use is often accompanied by an increased risk for residual cardiovascular events. In the MRC/BHF study, although a 24%

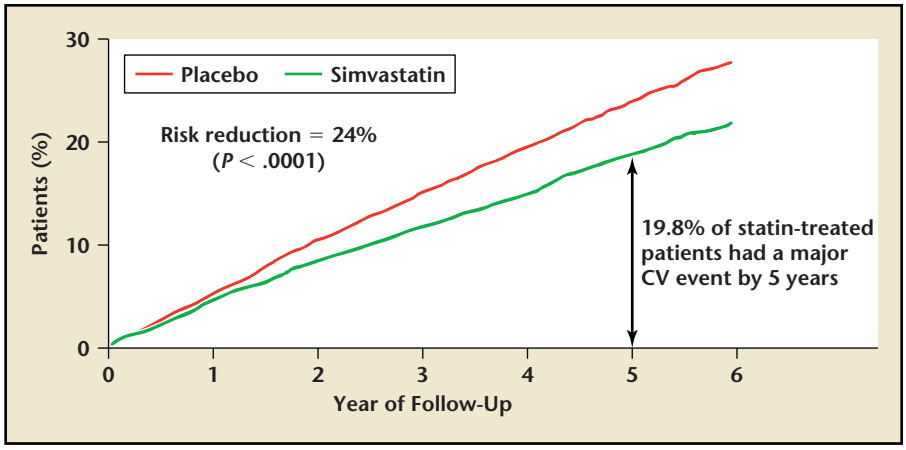


Figure 1. *Residual cardiovascular risk in the Heart Protection Study. CV, cardiovascular. Reprinted with permission from the Heart Protection Study Collaborative Group.*[9] www.medreviews.com

reduction in the cardiovascular event rate was demonstrated in the simvastatin group, there were 898 nonfatal MIs among the 10,269 patients randomized to simvastatin compared with 1212 in the 10,267 patients allocated to placebo (Figure 1). This means that the risk of MI in the simvastatin group over the 5 years of treatment was 19.8%—a substantial residual risk for cardiovascular events. In the TNT study, despite the cardiovascular benefit, there was no difference in overall mortality between treatment groups, and the higher dose was associated with a greater incidence of elevated aminotransferase levels. Although the event rates in the TNT trial were lower than those in other studies with similar populations, a significant percentage of residual risk remained. Safety limits seem to have been reached with the higher statin doses.

ACE Inhibitors and Cardiovascular Risk Reduction

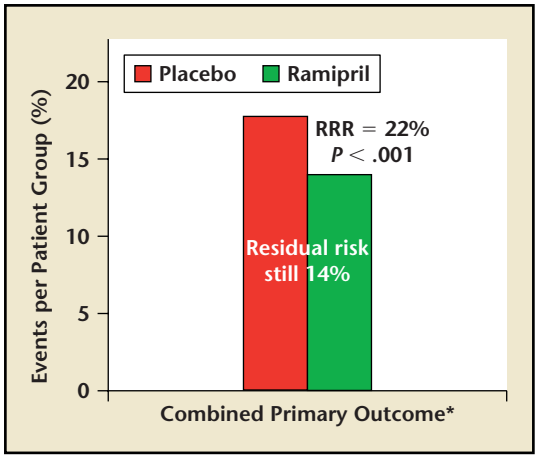
ACE inhibitors are thought to reduce cardiovascular events by blocking the renin-angiotensin system, although the mechanisms by which they might have an effect beyond blood pressure reduction are not fully understood. The Heart Outcomes Prevention Evaluation (HOPE) study was a landmark in demonstrating the potential role of ACE inhibitors in cardiovascular risk reduction.[13] In HOPE, 9297 participants with vascular disease or diabetes plus 1 other cardiovascular risk factor were randomized to an ACE inhibitor or placebo for a mean of 5 years. The primary endpoint for the study was a composite of MI, stroke, and death from cardiovascular causes. This endpoint was reached in 651 (14%) of the ACE inhibitor patients and 826 (17.8%) of the placebo patients, representing a 22% risk reduction. There were also significant reductions for the ACE inhibitor group in cardiovascular deaths (−26%), MI (−20%), all-cause mortality (−16%), revascularization procedures (−15%), cardiac arrest (−37%), heart failure (−23%), and diabetes complications (−16%).

Recent meta-analyses of ACE inhibitors indicate an overall benefit in terms of cardiovascular endpoints and mortality reduction with ACE inhibitors in patients with coronary artery disease and no left ventricular systolic dysfunction.[14,15] However, as with the statin studies, a significant residual risk for cardiovascular disease still exists with ACE treatment. In the HOPE study, despite risk reduction with treatment, 14% of ACE-inhibitor–treated patients reached the composite endpoint during the observation period, with a 9.9% risk for MI (Figure 2).

Combined Treatment Approaches to Cardiovascular Risk Reduction

Multifactorial interventions might seem to hold the most promise for reducing risk of cardiovascular events, as was demonstrated in the Steno-2 study.[16] In this study of patients with type 2 diabetes and microalbuminuria, conventional treatment was compared with a stepped approach that included intensive

Figure 2. *Residual cardiovascular risk in the HOPE Study. *The occurrence of cardiovascular death, MI, and stroke. RRR, relative risk reduction; MI, myocardial infarction; HOPE, Heart Outcomes Prevention Evaluation. Data from Yusuf S et al.*[13] www.medreviews.com



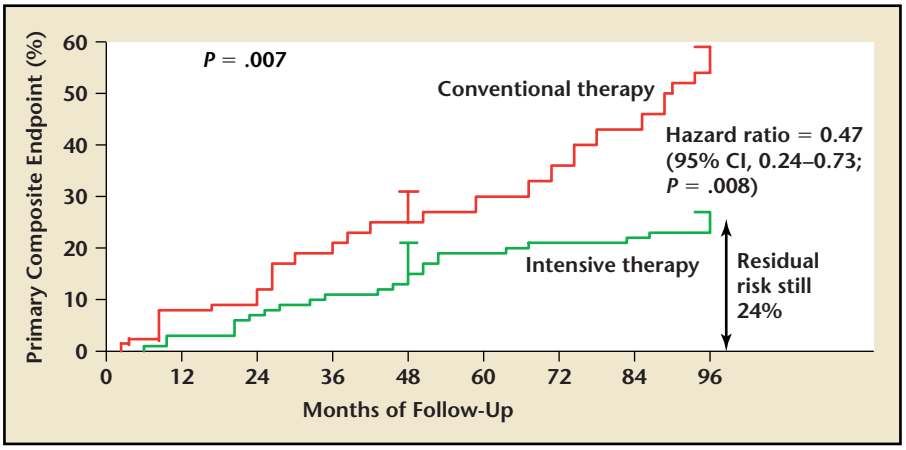


Figure 3. *Residual cardiovascular risk in the Steno-2 study after intensive risk management in patients with type 2 diabetes. CI, confidence interval. Reprinted with permission from Gaede P et al.[16] Copyright © 2003 Massachusetts Medical Society. All rights reserved.* www.medreviews.com

behavioral modification; pharmacologic therapies targeting dyslipidemia, hyperglycemia, hypertension, and microalbuminuria; and aspirin. The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization, and amputation. After a mean follow-up of 7.8 years, patients receiving intensive therapy had a 47% reduced risk of cardiovascular disease compared with those receiving usual care. However, the residual risk of a cardiovascular event was still 24% in the intensively treated group (Figure 3).

Potential Sources of Residual Risk

Some of the sources of residual risk, such as genetics and epigenetic phenomena, are not easily modifiable. Still, the risk imposed by these factors may be lowered by implementation of dietary, behavioral, and pharmacologic interventions.

Abdominal obesity is an interesting potential target for cardiovascular risk reduction and has much to recommend its adoption into routine practice. It can be easily and inexpensively assessed in the clinic by measuring waist circumference (WC). There is strong clinical evidence to support a role of WC in predicting the risk of cardiovascular and metabolic diseases. Several large trials demonstrate a strong correlation between WC and risk for MI.[17,18] In an 8-year follow-up of participants in the Nurses' Health Study, a greater WC and waist-to-hip ratio were independently associated with an age-adjusted risk for coronary heart disease.[19] In the HOPE study, a strong positive association between increased WC (third tercile) and increased risk of MI (23%), heart failure (38%), and total mortality (17%) was observed.[17] Furthermore, in the Health Professionals Follow-Up Study, there was a strong correlation between WC and type 2 diabetes, with relative risk increasing from 1.0 to 4.5 across WC quintiles.[18]

Additional risk factors could also be targeted. There is interest in markers of inflammation, such as C-reactive protein, for predicting cardiovascular risk and as potential targets for intervention.[20,21] There is also growing evidence that the assessment of apoA-1 and apoB levels, as well as the apoB to apoA-1 ratio, is important. In fact, the measurement of apo may provide more information than does the measurement of cholesterol fractions because the measurement of apoA-1 provides information about antiatherogenic particles (HDL cholesterol) and of apoB allows assessment of the total number of atherogenic particles (LDL cholesterol, very low-density lipoprotein cholesterol, and intermediate-density lipoprotein).[22] Currently, there is abundant evidence to support the concept that the ratio of apoB to apoA-1 could be the best marker for cardiovascular disease risk from an epidemiologic perspective, although this measurement has not made its way into risk management guidelines.[23] For example, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the apoB/apoA-1 ratio was the best on-treatment predictor of cardiovascular events.[24] In the INTERHEART study, the strongest risk factors for MI were smoking and the apoB/apoA-1 ratio.[3] The Apolipoprotein-related Mortality Risk Study (AMORIS) revealed that the measurement of apoB and apoA-1 improved the prediction of fatal MI at all levels of total cholesterol, LDL cholesterol, and triglycerides.[25] However, not all studies have demonstrated this relationship,[26] and work is needed to establish cut points and standard assays before these measures can be incorporated into the clinic.[27]

The approach to cardiovascular risk reduction should extend beyond the lowering of LDL cholesterol to also target known risk factors such as hypertension, hyperglycemia, and abdominal obesity. We should also remember to target health behaviors, such as smoking cessation, and not focus solely on pharmacotherapy. Ideally, pharmacologic approaches would reinforce positive health behaviors.

Clustering of Risk Factors Around Abdominal Obesity

The tendency for cardiovascular risk factors to cluster has long been

observed; the concept is known as "metabolic syndrome," a term proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III to focus physicians' attention on the importance of therapeutic lifestyle changes to prevent the development of type 2 diabetes and to reduce risk for cardiovascular disease.[28] Since the 2001 publication of the NCEP ATP III criteria[29] for metabolic syndrome, the concept has gained acceptance among US clinicians. It seems to be a practical way for physicians to discuss the health risks of abdominal obesity, with its associated excess of visceral fat,[30] and the health benefits of weight management. The current requirement for diagnosis of the metabolic syndrome according to NCEP criteria is the presence of 3 of the following 5 criteria:

- WC greater than 40 inches in men and greater than 35 inches in women.
- Triglycerides 150 mg/dL or higher.
- HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women.
- Fasting glucose 100 mg/dL or higher.
- Blood pressure 130/85 mmHg or higher.

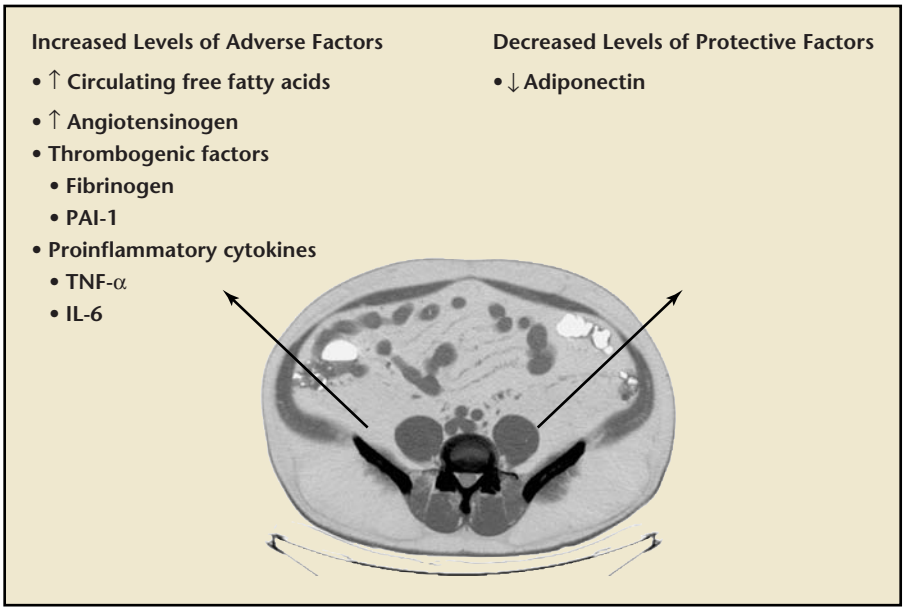
It should be noted that the concept of metabolic syndrome is currently the subject of intense medical debate. It has been suggested that the term "syndrome" falsely implies a clear pathophysiology for cardiovascular disease, and critics believe the current risk factor management guidelines should not be disregarded in favor of a sole focus on metabolic syndrome. Some experts suggest that small dense LDL particles, proinflammatory markers, prothrombotic markers, hyperuricemia, microalbuminuria, and endothelial dysfunction must also be included in the cluster of risk factors.[31] Although criteria for metabolic syndrome differ according to whether it is defined by the National Health and Nutrition Examination Survey III,[32] the NCEP ATP III,[29] the American Heart Association,[33] or the International Diabetes Federation,[34] abdominal obesity is consistently listed as a significant risk factor for cardiovascular disease.

Abdominal Obesity and Cardiovascular Risk

Increased abdominal fat deposition has been shown to be associated with insulin resistance and adverse effects on glycemic control,[35] increased levels of triglycerides and decreased levels of HDL cholesterol,[36] increased carotid artery stiffness,[37] oxidized LDL, and markers of inflammation.[38] Thus, it is not surprising that abdominal obesity has been associated with increased risk for diabetes, cardiovascular disease mortality, and all-cause mortality.[39,40] Although the last decade has expanded our understanding of the biology that underlies obesity and its comorbidities, the mechanism(s) by which abdominal fat accumulation might promote the development of these pathologies is not fully understood. However, recently it has become clear that adipose tissue is an active endocrine organ.[41] It is a source of numerous proteins, including leptin; prothrombotic products, such as plasminogen activator inhibitor-1 and fibrinogen; proteins of the renin-angiotensin system; and proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6; as well as the beneficial insulin-sensitizing hormone adiponectin.[41]

Furthermore, visceral fat located within the abdominal cavity is associated with the production of a more harmful profile of the above-mentioned products[41] and an adverse endocrine profile (Figure 4). In addition to the lipotoxicity inherent in increased levels of adipose tissue, part of the adverse health effects of visceral adiposity may be due to the

Figure 4. *Visceral adiposity and promotion of cardiovascular risk: increased abdominal adiposity is associated with an adverse endocrine profile. PAI, plasminogen activator inhibitor; TNF-α, tumor necrosis factor alpha; IL, interleukin. Image courtesy of Steven Smith, MD, Pennington Biomedical Research Center, Baton Rouge, LA.* www.medreviews.com



increased levels of free fatty acids in the portal vein that result in an adverse qualitative and quantitative lipid profile (small dense LDL cholesterol particles and lowered HDL cholesterol), as the liver is bathed in free fatty acids.

Weight Loss

There is a strong desire for slimness in the Western culture. In the United States, 24% of men and 28% of women are trying to lose weight. Among the obese, the rates are 50% of men and 58% of women.[42] Despite the desire to maintain a healthy weight, most Americans find it difficult to do so. Recently, the American Heart Association released a review outlining the clinical implications of obesity on cardiovascular health. It suggested that diet, physical activity, and behavior modification are equally important strategies for weight loss, with no clearly superior macronutrient or other dieting strategy.[43] Although losing weight and maintaining weight loss are difficult, even a loss of 5% to 10% of body weight is likely to produce improvements in a host of cardiovascular risk factors.

Weight Loss: Helpful or Harmful?

The health risks of being overweight or obese include a shortened life expectancy[44]; increased mortality[45]; and increased risk for diabetes, cardiovascular disease, and most cancers.[46] Weight loss has been shown to improve cardiovascular risk factors; it is associated with improvement in blood pressure[47] and lipids.[48] It also reduces morbidity. Furthermore, weight loss was shown to prevent type 2 diabetes in the Diabetes Prevention Program.[49] Despite these benefits, there is some debate over the role of weight loss in improving mortality rates, since a number of observational epidemiologic studies have linked weight loss with increased mortality.

The Framingham Heart Study is one of many studies showing that weight loss is associated with increased mortality.[50] Over an observation period of 20 years, and omitting deaths in the first 4 years, death rates were highest for subjects who lost weight, even when the data were adjusted for age, body mass index (BMI), smoking, and other risk factors. Compared with subjects whose weight did not change, the increase in total mortality rates was 44% in men who lost weight and 38% in women who lost weight. Other studies have demonstrated that this relationship exists whether the individual is overweight, normal weight, or underweight.[51]

However, studies that factor intentional weight loss demonstrate different results. For example, an analysis from the American Cancer Society's Cancer Prevention Study I reported intentional weight loss by 34% of the cohort.[52] After adjustment for initial BMI, sociodemographic factors, health status, and physical activity, intentional weight loss was associated with a 25% reduction in total mortality (rate ratio, 0.75) and a 28% reduction in mortality from cardiovascular disease and diabetes (rate ratio, 0.72).

The issue of weight loss and mortality is currently being addressed in a large-scale, long-term, controlled clinical trial in the Action for Health in Diabetes (Look AHEAD) study.[53] This study, funded by the National Institutes of Health, aims to assess the long-term effects of an intensive weight loss program delivered over 4 years in 5000 overweight and obese patients with type 2 diabetes. Patients in the intervention group are in an intensive lifestyle program designed to achieve and maintain weight loss through dietary modification and increased physical activity, with a weight loss goal of 10%. The control group receives diabetes education and support coupled with standard care from a primary care practitioner. The primary hypothesis of Look AHEAD is that over the 11.5-year follow-up, the lifestyle intervention program will have reduced the incidence of the first post-randomization occurrence of a composite outcome (cardiovascular death, nonfatal MI, and stroke) compared with the control group. Results from this trial are expected in 2012. Assuming an annual event rate of slightly more than 2%, the study is powered to detect an 18% relative decrease in the rate of primary outcomes in the lifestyle intervention group with 11.5-year follow-up.[53]

Shifting Emphasis From Weight to WC in the Clinic

One of the significant observations from the Diabetes Prevention Program[49] was the pronounced effect of *modest* weight loss.[49] With only 7% weight loss from baseline, there was a 58% reduction in risk of progression from impaired glucose tolerance to type 2 diabetes. Similarly, studies have shown that weight loss of 5% to 10% is associated with improvement in blood pressure and lipids.[47,48] The proposed explanation for the remarkable impact of modest weight loss on reducing risk factors and diabetes risk concerns the mobility of visceral adipose tissue stores. A 10% reduction in body weight has been associated with a 30% reduction in visceral adipose tissue.[54] This correlation is most likely the reason that outcomes for cardiovascular risk factors and glycemic control are so positive when obese persons lose 5% to 10% from baseline weight. They are still obese, but their visceral adipose tissue depot has been reduced dramatically, with resultant risk

factor benefits. Also, fat is the source of an insulin-sensitizing hormone, adiponectin, the levels of which have been shown to beneficially increase as fat mass decreases.[41]

However, weight loss alone is not guaranteed to improve risk factors, as has been demonstrated in an experiment evaluating large-volume liposuction.[55] In that study, 15 obese women were evaluated before and 10 to 12 weeks after liposuction; abdominal subcutaneous adipose tissue was decreased by an average of 44% (a loss of 9.1 kg of fat) in 8 women with normal glucose tolerance and by 28% (a loss of 10.5 kg of fat) in 7 women with type 2 diabetes. Liposuction did not significantly affect blood pressure, plasma glucose, insulin, or lipid concentrations in either group, nor did it affect C-reactive protein, adiponectin, tumor necrosis factor-α, interleukin-6, or insulin sensitivity.

Conclusion

Although progress has been made in utilizing the current therapeutic strategies to reduce risk for cardiovascular events, there still remains a significant residual risk that can be addressed to maximize impact. In this regard, abdominal obesity has been demonstrated to be a key element in the cluster of risk factors that are linked to increased risk for cardiovascular diseases and type 2 diabetes. Therefore, including the assessment of WC as a simplified way to measure abdominal obesity could add synergy to current treatment algorithms for cardiometabolic risk reduction. Hence, the goal is not to replace the current focus on the use of statins, ACE inhibitors (or angiotensin-2 receptor blockers), aspirin, and smoking cessation; rather, the goal is to expand the focus to include other factors, such as the reduction of WC in overweight and obese individuals, as a complement to our current therapeutic strategies for the reduction of cardiometabolic risk. ■

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Main Points

- Approaches to cardiovascular risk reduction should extend beyond the focus on low-density lipoprotein cholesterol levels and pharmacotherapy with angiotensin-converting enzyme inhibitors or statins, and should also target known risk factors such as hypertension, hyperglycemia, and abdominal obesity.
- Some of the sources of residual risk, such as genetics and epigenetic phenomena, are not easily modifiable. However, dietary, behavioral, and pharmacologic interventions may lower the risk imposed by these factors.
- Abdominal obesity has been associated with increased risk for diabetes, cardiovascular disease mortality, and all-cause mortality, and is an appropriate target for reducing cardiovascular risk.
- A 10% reduction in body weight has been associated with a 30% reduction in visceral adipose tissue. This is most likely the reason that outcomes for cardiovascular risk factors and glycemic control are so positive when obese persons lose 5% to 10% of baseline weight.

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