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Point/Counterpoint

Weight Loss Is a Useful Therapeutic Objective

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See article by Després, pages 216-222 of this issue.

ABSTRACT

Overweight/obesity has been associated with increased risk for several conditions, including hypertension, hypercholesterolemia, diabetes mellitus, heart disease, and stroke. The morbidity associated with overweight and obesity translates into excess mortality risk, which is observed even when increased weight is not associated with metabolic abnormalities. The achievement of moderate weight loss, regardless of the treatment strategy, is associated with favorable clinical outcomes, including significant reduction in the incidence of type 2 diabetes and blood pressure levels. These data suggest that weight loss might be a useful therapeutic objective in the prevention and management of comorbidities associated with overweight/obesity.

RÉSUMÉ

La surcharge pondérale et l'obésité ont été associées à une augmentation du risque de nombreuses affections, à savoir l'hypertension, l'hypercholestérolémie, le diabète, la cardiopathie et l'accident vasculaire cérébral. La morbidité associée à la surcharge pondérale et à l'obésité aboutit à un risque de surmortalité, qui est observé même lorsque l'augmentation du poids n'est pas associée à des anomalies métaboliques. Quelle que soit la stratégie de traitement, la perte de poids modérée est associée à des résultats cliniques favorables, y compris une réduction importante de l'incidence du diabète de type 2 et des valeurs de la pression artérielle. Ces données suggèrent que la perte de poids serait un objectif thérapeutique utile à la prévention et à la prise en charge des comorbidités associées à la surcharge pondérale et à l'obésité.

Obesity and Health Outcomes: Observational and Epidemiologic Data

The concept that increased body mass index (BMI), particularly in the ranges classified as overweight (BMI $\geq$ 25 kg/m^2 and $<$ 30 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2), leads to health hazards is well established.[1-7] Previous reports have clearly demonstrated an association between increased BMI and diverse adverse outcomes. In fact, compared with normal weight, being overweight or obese has been associated with increased risk for several conditions, including hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, sleep apnea, degenerative joint disease, infertility, and certain cancers (ie, cancers of the esophagus, colon, liver, gallbladder, and pancreas).[1-9] Of interest, data from the Framingham Heart Study showed that weight gain after the young adult years conveyed an increased risk of cardiovascular disease in both sexes that could not be attributed either to the initial weight or to the levels of the risk factors that may have resulted from weight gain, suggesting that obesity is an independent risk factor for heart disease.[10] Moreover, the morbidity associated with overweight and obesity translates into excess mortality risk as evidenced by comprehensive population-based studies.[11-14] Most notably, a large prospective study involving 1.46 million white adults demonstrated a stepwise increment in total mortality across categories of BMI that ranged from a hazard ratio (HR) of 1.13 in overweight individuals to a HR of 2.51 in individuals with severe obesity (BMI $\geq$ 40 kg/m^2) when compared with normal weight.[11]

Despite being highly correlated with percentage of body fat and widely used as the measure of obesity,[15] assessment of adiposity by BMI does not directly assess the body composition, in particular abdominal obesity and visceral fat content. In this context, it has been observed that for any given BMI, increased abdominal fat is associated with increased risk for the development of cardiovascular disease.[16] In addition, in a study of 27,098 participants, abdominal obesity assessed by waist-to-hip ratio was a stronger predictor of myocardial infarction than was BMI alone.[17] These results suggest that additional characterization of adiposity, specifically the identification of abdominal obesity, may have an even more pronounced adverse impact on future outcomes.

It should be recognized, however, that increased weight may not cause evident metabolic abnormalities in some individuals. In this context, previous reports have focused on a unique group of individuals with an apparently normal

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metabolic profile despite being overweight/obese—so-called metabolically healthy obesity or benign obesity.[18] This condition, however, has recently proved to be not quite so harmless.[19,20] In a recent meta-analysis of 8 studies that included 61,386 persons, individuals with metabolically healthy obesity (ie, BMI $\geq$ 30 kg/m^2 and one metabolic syndrome component disorder or less) had a 24% increment in all-cause mortality plus cardiovascular events over the long term (> 10 years of follow-up).[19] In addition, this study demonstrated that blood pressure, waist circumference, and insulin resistance increased and high-density lipoprotein cholesterol decreased across the BMI categories (from normal weight to overweight to obese) regardless of the metabolic status. In parallel to these results, other studies suggested that these individuals with increased weight and normal metabolic profiles also have a greater prevalence of subclinical coronary atherosclerosis as assessed by coronary artery calcification and a higher incidence of type 2 diabetes compared with metabolically healthy normal-weight participants.[21,22] In addition, using a more stringent definition of health, another study observed increased cancer mortality in healthy obese individuals.[23] This body of evidence suggests that there is not a healthy pattern of obesity. Further supporting this concept, a recent report suggests that even the physiological weight gain of pregnancy can lead to an adverse cardiometabolic profile as early as 1 year postpartum if not reversed.[24] It thus emerges that increased weight is consistently associated with adverse conditions, which suggests that weight loss may be a useful therapeutic goal.

Weight Loss and Health Outcomes

The achievement of moderate weight loss regardless of the treatment strategy (ie, lifestyle, medication, or bariatric surgery) has been associated with favorable clinical outcomes as demonstrated by several studies.

Weight loss and cardiovascular risk factors

In the Diabetes Prevention Program (DPP) study, a weight loss of 7% with lifestyle and physical activity reduced the progression from glucose intolerance to diabetes by 58% over 3 years of follow-up.[25] Moreover, in the DPP cohort, this beneficial impact of weight loss was maintained over 10 years of follow-up.[26] A positive impact of weight loss on hypertensive individuals has also been reported. In a meta-analysis of 46 studies, participants treated with a weight-loss diet had a reduction in systolic blood pressure (SBP) of 6.3 mm Hg at 1 year of follow-up, which was also significant in participants treated with the weight-loss medication orlistat, in which the decrement in SBP was 2.5 mm Hg.[27,28] Indeed, this analysis demonstrated that the loss of only approximately 4 kg was needed to achieve a reduction of 6 mm Hg in SBP in studies using the dietary intervention.[27] The severity of sleep apnea, which is another condition associated with increased cardiovascular risk, has also been shown to improve with modest weight loss in obese individuals.[29] Confirming the beneficial impact of weight loss on cardiovascular profile, a report of the lifelong impact of BMI categories (normal weight, overweight, and obesity) in 3217 individuals with serial assessment of cardiovascular risk factors, adiposity, and carotid intimal media thickness demonstrated that participants who dropped a BMI category in adulthood had lower carotid intimal media thickness (−0.034 mm) and leptin concentrations (−0.4 ng/mL), even when this change was not maintained, compared with participants who never lost weight.[30] These results suggest that losing weight, even if not sustained, might result in long-term cardiovascular benefit.

Weight loss and additional outcomes

Weight loss in overweight/obese individuals also has positive effects beyond the cardiovascular risk profile. In obese women, weight loss is associated with improvement in fertility by re-establishing menstrual regularity and ovulation.[31] Another report demonstrated a significant reduction in knee-joint load in overweight and obese older adults who underwent lifestyle intervention, suggesting that each pound of weight lost results in a 4-fold reduction in the load exerted on the knee per step.[32] In addition, in a study of 332 overweight/obese adults, a structured weight loss program led to complete resolution of symptoms of gastroesophageal reflux disease in 65% of the participants.[33] Reducing weight also has a positive impact on mental health, because losing weight is associated with reduction in the symptoms of depression experienced by obese individuals.[34]

Randomized Clinical Trials on the Impact of Weight Loss on Mortality and Cardiovascular Events

Despite the abundant literature supporting the positive effect of weight loss on several outcomes, data on the impact of weight loss on mortality and cardiovascular events are less convincing. A positive effect, however, has been suggested. In a prospective study of 4869 men aged 56-75 years followed for 7 years, participants who intentionally lost weight had a reduction in all-cause mortality (relative risk, 0.59).[35] Similarly, in a clinical trial of 318 older overweight/obese adult with knee osteoarthritis who were randomized to a weight-loss intervention or a control group and followed for 8 years, the total mortality was 50% lower in those assigned to the weight-loss intervention group.[36] A recent randomized trial (Action for Health in Diabetes [Look AHEAD]) designed to compare an intensive lifestyle intervention with standard diabetes education in individuals with diabetes and overweight/obesity (N = 5145; follow-up, 9.6 years) did not show a difference in the primary outcome of fatal and nonfatal cardiovascular events between the groups. However, the intensive lifestyle intervention led to greater reduction in glycated hemoglobin and greater initial improvement in fitness and all cardiovascular risk factors, except low-density lipoprotein cholesterol levels.[37] Of note, the difference in weight loss between the groups at the study end was only 2.5%, which could have impacted the results by reducing the likelihood of a difference in cardiovascular events. In addition, post hoc analyses of this study found a beneficial effect of the intensive lifestyle intervention on depression and health-related quality of life,[38] urinary incontinence in men,[39] and sexual function in women.[40]

Brief Overview of Current Strategies for Weight Loss

The achievement of sustained weight reduction is 1 of the most challenging goals in health care because the long-term