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Point/Counterpoint

Obesity and Cardiovascular Disease: Weight Loss Is Not the Only Target

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See article by Kramer, pages 211-215 of this issue.

ABSTRACT

Although obesity is generally perceived as causing prejudice to heart health, there is considerable individual metabolic heterogeneity among equally overweight or obese individuals. Such heterogeneity suggests that several factors can modulate health risk at any given body weight. In the present article, the thesis that weight loss and achieving a healthy body weight through caloric restriction might not represent optimal clinical and public health messages to combat the current obesity epidemic is defended. Rather, it is proposed that reducing waist circumference and increasing cardiorespiratory fitness through improving nutritional quality, reducing sedentary behaviours, and increasing participation to physical activity/exercise might be associated with clinical benefits, sometimes even in the absence of weight loss.

RÉSUMÉ

Bien que l'obésité soit généralement perçue comme causant un préjudice à la santé cardiaque, il existe une hétérogénéité métabolique individuelle considérable entre les individus montrant le même niveau de surpoids ou d'obésité. Cette hétérogénéité suggère que plusieurs facteurs peuvent moduler les risques pour la santé à tout poids corporel donné. Dans cet article, la thèse selon laquelle la perte de poids et l'atteinte d'un poids corporel sain grâce à la restriction calorique pourraient ne pas représenter des messages cliniques et de santé publique optimaux pour lutter contre l'épidémie d'obésité actuelle est défendue. I est plutôt proposé que la réduction du tour de taille et l'augmentation de la capacité cardiorespiratoire par l'amélioration de la qualité nutritionnelle, la réduction des comportements sédentaires, et une participation accrue à l'activité physique/exercice pourraient être associées à des bénéfices cliniques, parfois même en l'absence de perte de poids.

The epidemic of obesity has received a lot of attention and is considered as a key driver behind the rapidly growing prevalence of type 2 diabetes worldwide.[1] For instance, it is estimated that there are already more than 371 million individuals with type 2 diabetes worldwide and its prevalence has reached a stunning 114 million of individuals in China.[2] For decades, epidemiological studies have shown that obesity is associated with increased morbidity and mortality.[3] For that reason, it has been assumed that weight loss and achieving a "healthy body weight" would reduce morbidity and increase longevity in overweight and obese patients.[4]

Defining Obesity: Limitations of the Body Mass Index

The most commonly used anthropometric index to make a diagnosis of obesity has been a legacy of the late Ancel Keys, who provided evidence that the body mass index (BMI) (expressed as weight in kg/height in m^2) was related to body fat content and associated comorbidities.[5] Since then, many large prospective observational studies have shown a relationship between the BMI and mortality. However, although it is clear that a very high BMI increases mortality, the shape of the relationship between the BMI and mortality remains controversial. For instance, in a report that has received a lot of media attention, Flegal et al.[6] published in the *Journal of the American Medical Association* evidence from a large meta-analysis involving almost 3 million individuals with 270,000 deaths that overweight was associated with reduced mortality whereas class I obesity (BMI from 30 to 35) was not associated with an increased mortality compared with the so-called normal-weight reference group (BMI from 18.5 to 25). These observations left the media quite perplexed and the population confused regarding the effect of obesity on health. However, in an elegant editorial accompanying report

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from Flegal et al., Heymsfield and Cefalu[7] identified a number of important factors which could explain this apparent protection conferred by overweight/moderate obesity. In addition to making the point that Flegal et al. did not control for individual differences in body muscle mass content, level of physical activity and fitness, nutritional quality, and regional body fat distribution, Heymsfield and Cefalu raised the important issue that the BMI reference group used in the analysis included individuals with BMI values as low as 18.5. As illustrated in Figure 1, an analysis from the **E**uropean **P**rospective **I**nvestigation into **C**ancer and Nutrition (EPIC) study conducted on 125,000 men followed for almost 10 years, the lowest mortality risk is observed at BMI values around 24-25 and not at 19-20 where mortality risk is actually increased.[8] In other words, although a BMI of 20 might be normal for a 20-year-old adult, it might rather represent frailty and sarcopenia in a 65- to 70-year-old individual. In addition, individuals with very low BMI values also include those who have lost weight due to existing or subclinical chronic diseases and some current and past smokers. Thus, most middle-aged, physically active and fit individuals do not have a BMI of 19-20. It is therefore not surprising that this BMI category is associated with increased mortality, which represents reverse causation or confounding biases. It would therefore be important for Flegal et al. to redo their analyses using the BMI associated with the lowest mortality rate as the reference group and not include the higher-risk very low BMI subjects.

Studies have also shown that obese patients receive more medical attention, which might also obviously contribute to modulate their mortality risk compared with nonobese individuals.[9] In that regard, the Emerging Risk Factor Collaboration group[10] has also shown that obesity per se, measured either using the BMI, waist circumference, or the waist-to-hip circumference ratio did not predict cardiovascular events after control for intermediate risk factors (blood pressure, lipids, diabetes). At first glance, these results might suggest that to reduce cardiovascular disease (CVD) risk in obesity, it would be more important to treat the related risk factors than to treat excess adiposity. However, a closer look at the results of this study revealed that adiposity indices, particularly abdominal adiposity, were strongly correlated with intermediate risk factors, showing again the importance of paying attention to the upstream driver of altered risk factors: obesity.

Beyond the BMI: Body Shape Matters

Another aspect that can no longer be ignored in 2013 considering the abundant literature available is the importance of considering individual differences in regional body fat distribution.[11,12] Almost 25 years ago, we reported that there are remarkable differences in the way people accumulate energy in regional adipose tissue depots.[13] We now have considerable evidence from several large cardiometabolic imaging studies that among equally overweight or obese individuals, those with a selective excess of intra-abdominal or visceral adipose tissue (such as the subject in the top panel of Fig. 2) are those who are also at greater risk of being characterized by a whole constellation of atherogenic and diabetogenic abnormalities often referred to as the metabolic syndrome or the insulin resistance syndrome.[15-18]

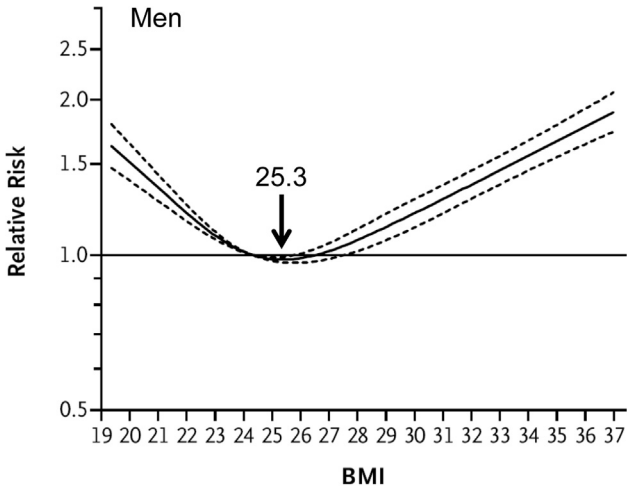

Figure 1. Relative risk of death over a 9.7-year follow-up among men (n = 125,000) of the European Prospective Investigation into Cancer and Nutrition (EPIC) study according to body mass index (BMI) categories. Solid lines indicate relative risks, and dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 25th, 75th, and 95th percentiles of the sex-specific distribution of each anthropometric variable. The reference point for BMI is the midpoint of the reference group (23.5 to < 25.0) from categorical analysis. The graphs are truncated at the 1st and 99th percentiles. Age was used as the underlying time variable in the regression models, with stratification according to centre and age at recruitment and additional adjustment for smoking status, educational level, alcohol consumption, physical activity, and height. The relative risks are plotted on a logarithmic scale. Reproduced from Pischon et al. (page 2110).[8] Copyright © 2008 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Several factors affect the way we put on regional fat including genetic factors, diet composition, and importantly, lack of vigorous physical activity, just to name a few key variables (Fig. 3).

Body Fat Distribution and Health: The Notion of Ectopic Fat

In that regard, we have recently published results from a large international cardiometabolic imaging study involving 4144 patients from 29 countries in which we assessed using computed tomography abdominal visceral adiposity at L4-L5 and estimated liver fat content on the basis of liver density (the latter variable being expressed in Hounsfield units: the lower the liver density, the greater the liver fat content).[18,19] As also reported in the Dallas Heart Study,[20] we found in men and women a highly significant relationship between abdominal visceral adiposity and liver fat content, patients with type 2 diabetes having more visceral adipose tissue and liver fat for any given BMI.[18,19] Furthermore, odds ratios for type 2 diabetes revealed that a 1 SD increase in visceral adiposity was independently associated with type 2 diabetes whereas a 1 SD increase in liver density (reflecting a leaner liver) was independently but negatively associated with type 2 diabetes. After control for visceral adiposity and liver fat, there was no relationship between subcutaneous adiposity and type 2 diabetes.[20]