Obesity and Pulmonary Embolism: Can We Dismantle the "Obesity Paradox"

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Obesity is a complex medical condition influenced by genetics, diet, physical activity level, sleep, medication, and psychosocial stress. Increased body mass can lead to increased adipose tissue dysfunction, which can adversely affect cardiovascular health. In the United States., 42% of adults are obese. An estimated $260 billion in direct medical costs is expended annually on obesity. Inpatient cost is 46% higher, and spending on prescription medications is 80% higher among these patients. Comprehensive lifestyle interventions integrate behavioral, dietary, and physical activity components. Their goal is to achieve and maintain weight loss of at least 5%. To date, patient education on dietary and physical activity recommendations has not slowed the rising obesity rates.[1]

Psychological damage from obesity can be traumatizing. Bullying, body-shaming, and ostracism are common, especially among teenage girls. The fear of obesity can lead to anorexia nervosa, the deadliest of all psychiatric illnesses. Sudden cardiac death is the most frequent cause of mortality among anorexics, and suicide is responsible for the second largest number of deaths in this population.

Americans are motivated to lose weight to improve their health, appearance, and social standing. In the United States, annual expenses exceed $66 billion for weight-loss products and programs. Nevertheless, about 80% regain the weight they had lost within 5 years. Statistics are less discouraging for bariatric surgery. About one-quarter regain all their lost weight by 10 years.

Weight stigma is rarely discussed, but its presence in the workplace is pervasive. Heavier people are paid and promoted less frequently than their thinner colleagues and are often stereotyped as lazy or undisciplined. Half of managers surveyed in a poll said they prefer interacting with "healthy weight" employees. Some companies have formed employee groups to raise awareness of fat bias. For example, Amazon employees formed a Body Positive Peer Group to highlight the corrosive effects of fat-shaming.[2]

The problem of overweight and obesity is global. General populations, as expected, show a strong correlation between increased weight and the presence of pulmonary embolism (PE). Indeed, various studies have shown the impact of obesity on the risk of venous thromboembolism (VTE).[3,4] While obesity per se is a risk, the added impact of prothrombotic genotypes has been reported from the Tromsø Study (1994–2012) and the Trøndelag Health Study (HUNT) (1995–2008).[5] In this issue of *Thrombosis & Haemostasis*, Frischmuth et al[6] report from Tromsø, Norway, a survey of 36,341 participants. They found that 38% were overweight (body mass index [BMI]: 25–30) and 14% were obese (BMI $>$ 30). These participants were followed for a median of 14 years. During that period, 1,051 VTE events occurred. The likelihood of suffering VTE was 40% greater with overweight and 86% greater with obesity. Overall, about 25% of all VTE events can be attributed to overweight and obesity in a general population from Norway.

Despite the link between high BMI and a range of chronic cardiovascular conditions, obesity is often associated with a reduced risk of mortality.[7] This observation is known as the "obesity paradox." Mechanisms may include adipose tissue's ability to absorb circulating toxic metabolites, provide better nutritional reserve, and facilitate more favorable immune function.[8] The international GARFIELD-VTE study of 10,869 participants with confirmed VTE followed these patients for 24 months. Almost 70% were overweight or obese. The proportion with PE rather than deep vein thrombosis was greater with each increasing BMI category. Obese patients more commonly remained on anticoagulants for at least 2 years compared to those with a normal BMI (52.3 vs. 37.7%). With respect to mortality, there was evidence of an "obesity paradox." In GARFIELD-VTE, after 24 months, the

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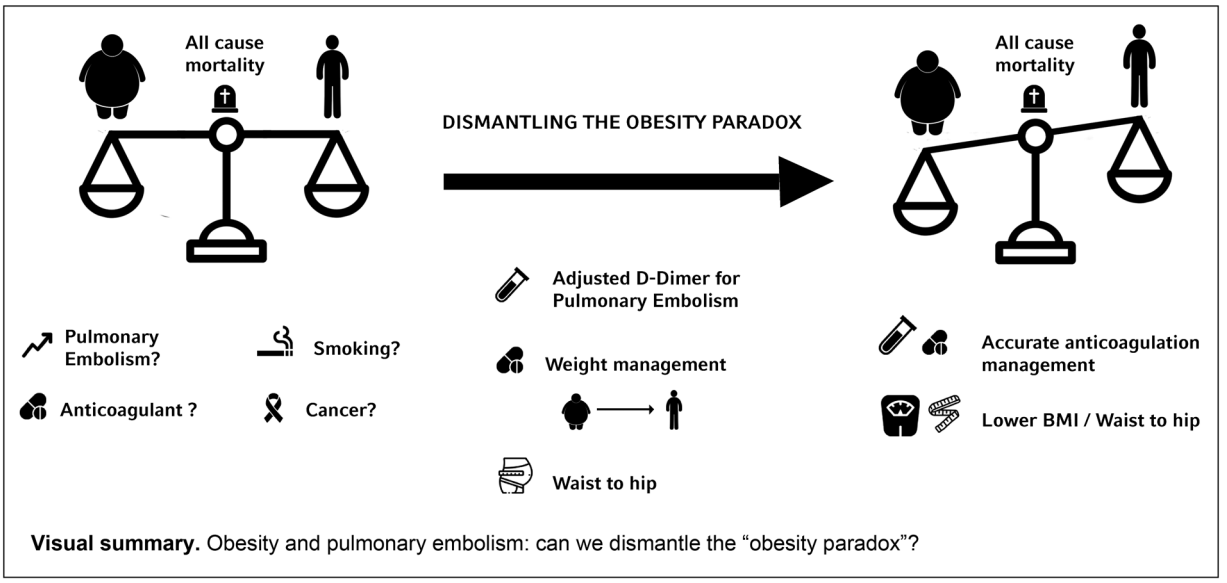

Visual summary. Obesity and pulmonary embolism: can we dismantle the "obesity paradox"?

risk of all-cause mortality was 25% lower in overweight and 41% lower in obese patients compared with those who had a normal BMI.[9]

In the Nurses' Health Study cohort of 112,822 women free of cardiovascular disease at baseline, prospective study for 16 years yielded 1,619,770 person-years of follow-up. Based on self-report and medical records, 280 cases of PE were documented, of which 125 were unprovoked. In multivariate analysis, obesity (RR = 2.9), heavy cigarette smoking (>25 cigarettes per day), and hypertension (RR = 1.9) were independent predictors of PE.[10]

Not all studies found an increased risk of PE among obese participants. In the APEX trial of 7,372 medically ill hospitalized patients at risk for PE, those patients with lower BMI had a higher VTE risk. Some of these medically ill patients had underlying cancer or frailty. Thus, this study informs us that the relationship between obesity and PE depends upon the population being studied.

In the current issue of Thrombosis and Haemostasis, Gaugler et al studied a cohort of 1,593 patients suspected of PE.[3] Their cohort was derived from the ADJUST-PE study and was used for the post-hoc analyses published in the current manuscript. ADJUST-PE was an international prospective diagnostic management outcome study.[11] In the Gaugler et al cohort, the median age was 59 years, and 56% of patients were women. Overall, 343 patients (22%) were obese, and 292 (18%) had a confirmed PE at initial presentation.

The study published today had two objectives: (1) to evaluate the accuracy of a diagnostic algorithm in obese versus nonobese patients that incorporated the combination of clinical pretest probability and an age-adjusted D-dimer cut-off in patients with a clinical suspicion of PE. Patients with high clinical probability of PE went directly to computed tomography (CT) pulmonary angiography. Those with low or intermediate clinical probability and an elevated D-dimer level also underwent CT pulmonary angiography. In contrast, those with low or intermediate clinical probability and a normal D-dimer were classified as "PE ruled out" and did not undergo further diagnostic testing for PE. (2) To evaluate the relationship between BMI and obesity.

The diagnostic algorithm worked equally well in obese and nonobese patients. In total, 132 obese patients had a non-high clinical probability and a normal age-adjusted D-dimer level. They were not anticoagulated for PE. During the 3-month follow-up, none of the obese patients had a confirmed PE. Similarly, 499 nonobese patients had a non-high clinical probability, a normal age-adjusted D-dimer level, and were not anticoagulated for PE. None of the nonobese patients had a confirmed PE during the 3 months of study follow-up. Thus, the age-adjusted D-dimer strategy appeared safe in excluding PE in both obese and nonobese patients with suspected PE.

Overall, BMI and obesity were not associated with confirmed PE. The adjusted relative risk (RR; 95% confidence interval [CI]) was 0.82 (0.62–1.07). The CIs were wide because of the low sample size. When BMI was examined by quintiles, the third [RR: 1.44 (1.03–2.05)] and fourth [RR: 1.45 (1.03–2.05)] quintiles did show a positive association between BMI and obesity. However, these sub-analyses are only suggestive, not conclusive.

Should we be using BMI for our principal definition of obesity? Probably not. In a cohort study of 387,672 participants from the UK Biobank, waist-to-hip ratio (WHR) was superior to BMI for predicting all-cause and cause-specific mortality. BMI assesses mass and general adiposity, whereas WHR assesses adiposity distribution. Current recommendations for optimal BMI range are inaccurate when applied broadly to individuals with varying body compositions.[12]

The relationship between BMI and mortality raises a critical question: by lowering BMI safely, can we reduce all-cause and cardiovascular mortality? Can we dismantle the obesity paradox? A new era of pharmaceutical successes is evolving with weight reduction medications that are far more effective and safer than their predecessors. The first drug approved for long-term weight management was

semaglutide, a potent glucagon-like peptide receptor agonist. In addition to weight loss, semaglutide has a multitude of additional favorable anti-inflammatory, metabolic, and hemodynamic effects. These include decreases in the C-reactive protein level, systolic blood pressure, and NT-proBNP level.

The STEP HFpEF trial studied 529 HFpEF patients with a BMI of 30 or greater. They were randomized to semaglutide 2.4 mg injected weekly versus placebo injections for 1 year. The semaglutide group compared with placebo had a larger reduction in symptoms, greater improvement in exercise function, and greater weight loss.[13]

The Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) study evaluated the effect of semaglutide versus placebo on major adverse cardiovascular events in participants with overweight or obesity and preexistent cardiovascular disease. Overall, 804 sites in 41 countries across six continents recruited 17,604 participants with overweight or obesity and established cardiovascular disease between October 2018 and March 2021. The primary objective of the double-blinded SELECT trial was to examine whether once-weekly subcutaneously injected semaglutide 2.4 mg is superior to placebo for reducing the incidence of a composite end point comprising cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.[14] On August 8, 2023, Novo Nordisk announced the topline results of SELECT. Semaglutide reduced by 20% the prespecified major adverse cardiovascular events of death, myocardial infarction, or stroke.[15]

Gaugler and colleagues have moved the field forward in their important study. They have demonstrated that regardless of a patient' weight, the workup for suspected PE should begin with assessment of clinical probability and with measurement of an age-adjusted D-dimer level. They did not obtain definitive results when trying to correlate obesity with PE. By unintentionally leaving this question open, they provide us with the possibility of scuttling previous dogma and, with effective weight management, scuttling the obesity paradox.

Conflict of Interest
None declared.

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