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Mechanisms, Pathophysiology, and Management of Obesity

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Mechanisms, Pathophysiology, and Management of Obesity

TO THE EDITOR: The review article by Heymsfield and Wadden (Jan. 19 issue)[1] is valuable with respect to the clinical management of obesity, but information about the contribution of mitochondrial genes to obesity is not included. Mitochondrial dysfunction is associated with an accumulation of fat that can occur during aging and in patients with obesity, the metabolic syndrome, or diabetes mellitus.[2]

Zheng et al.[3] found that obese participants with a high metabolic syndrome score have increased DNA methylation in the mitochondrial genes *MT-CO1* and *MT-ND6* and in the mitochondrion-related nuclear gene *PPARGC1A*. Flaquer et al.[4] conducted a study using samples obtained from 6528 participants in the KORA (Cooperative Health Research in the Region of Augsburg) studies and found that two mitochondrial single-nucleotide polymorphisms (SNPs) located in the cytochrome *c* oxidase subunit genes (*MT-CO1* and *MT-CO3*) and three mitochondrial SNPs located in the NADH dehydrogenase subunit genes (*MT-ND1*, *MT-ND2*, and *MT-ND4L*) were significantly associated with a higher body-mass index (BMI). Latorre-Pellicer et al.[5] systematically characterized conplastic mice (mice in which the nuclear genome of one mouse is backcrossed into the cytoplasm of another, so that the nuclear genes and mitochondrial genes are from different parents) throughout their lifespan. They found that the mitochondrial DNA haplotype profoundly influences mitochondrial proteostasis and generation of reactive oxygen species, insulin signaling, telomere shortening, the development of obesity, and mitochondrial dysfunction. These findings highlight the importance of the contribution of mitochondrial genetic variants to the risk of a high BMI.

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TO THE EDITOR: Heymsfield and Wadden identify environmental and genetic factors as well as energy-balance dysregulation as the leading mechanisms of obesity, and they describe therapeutic lifestyle changes, adjunctive pharmacotherapy, and bariatric surgery as the main treatment strategies for this condition. We would like to point out that emotional factors can influence overeating that results in overweight and obesity.[1]

Emerging data suggest that addictive overeating is a common experience of obese persons.[1] In one randomized trial, mothers had significant and clinically important reductions in weight when their school-age children were taught about nutri-

tion and influenced the family's dietary and physical activity habits.[2] We think that further research concerning these issues would be important and timely. Future findings regarding emotional factors, in general, and binge eating, in particular, may lead to important clinical and public health measures to combat the increasing pandemic of obesity that is a major contributor to the emergence of cardiovascular disease as the leading cause of death worldwide.[3,4]

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TO THE EDITOR: We challenge the recommendation by Heymsfield and Wadden that people who are overweight or obese should lose weight using a reduced-calorie diet. This recommendation assumes that obesity is the cause of metabolic dysfunction and that weight loss is the cure for metabolic dysfunction. We argue rather that obesity is a marker for metabolic dysfunction, and "real food"[1] is its cure.

If recommendations to lose weight with the use of a calorie-restricted diet were a drug, they probably would not receive FDA approval. The studies presented by the authors indicate that even high-intensity weight-loss interventions are ineffective in the long term and adverse effects such as stigmatization of and bias against obese persons are common.[2] Not surprisingly, many physicians and patients are frustrated by this approach.

The recommendation to improve metabolic health unrelated to weight loss can improve clinical end points (e.g., a Mediterranean diet reduces mortality from cardiovascular disease[3] and is more sustainable than other approaches). Finally, we physicians need to use our societal standing to advocate for change from obesogenic environments loaded with high-sugar, low-fiber foods[1] toward environments that make the healthy choice the easy choice.[4]

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TO THE EDITOR: Although they discuss the mechanisms and pathophysiological features of obesity, Heymsfield and Wadden do not emphasize the role of insulin, a metabolically important hormone. High levels of insulin inhibit lipolysis and suppress hepatic glucose production.[1] As a consequence, levels of plasma fatty acids and glucose are reduced. The deficiency of fuel in the blood induces intense hunger and physiological weakness, which in turn probably induce overfeeding and physical inactivity, leading to positive energy balance and eventual obesity.

Basal hyperinsulinemia is induced by a carbo-

hydrate-rich diet.[2] This is why a carbohydrate-rich diet is generally much more obesogenic than a fat-rich diet, which is more likely to induce basal hypoinsulinemia.[2] Diet is as important as environmental or genetic factors in inducing obesity.

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THE AUTHORS REPLY: We thank Sheu and colleagues for expanding our discussion to the role played by mitochondria in the pathogenesis and management of obesity. Mitochondrial mechanisms are directly involved in cellular energy production and are increasingly recognized as playing a role in the control of energy balance. A study of mitochondrial DNA has also identified genetic variants linked with excess adiposity and metabolic disturbances.[1]

We agree with Andreotti et al. that emotional factors play an important role in the genesis of overweight and obesity and that these effects should be the focus of additional research. In support of this viewpoint, longitudinal studies show that depression, anxiety, and life stress increase the odds of weight gain with the development of overweight and obesity through multiple as yet incompletely established mechanisms.[2] These effects are bidirectional, with obesity increasing the risk of depression and anxiety. Binge eating disorder, which is characterized by consumption of an objectively large amount of food and loss of control over eating, occurs in only a small percentage of obese persons who may also be at an increased risk for depression and anxiety. Studies are currently in progress to examine whether the concept of food addiction contributes to our understanding of and treatment approaches for disturbed eating behaviors and binge eating.[3]

We support Stigler and colleagues' call on physicians to serve as advocates for changing the nation's obesogenic food environment in favor of one that makes vegetables and fresh fruits available to all citizens. We also think that data are lacking on the possible health benefits, independent of weight loss, of diets with various macronutrient compositions aligned with the nutritional needs of patients with weight-related chronic diseases. Unlike Stigler et al., we think the data show that high-intensity lifestyle interventions, which include calorie restriction, reduce the short-term and long-term risks of type 2 diabetes and other health complications, even when lost weight is partially regained.[4]

Lee and Shin emphasize the important roles played by insulin in the pathogenesis of obesity and carbohydrate-rich diets in the management of this condition. South Korea, the home country of Lee and Shin, has a long history of a high carbohydrate intake from vegetables and fresh fruits, even though obesity rates are low.[5] We agree that excess intake of "added" sugars, particularly those in sweetened beverages, contributes to the pathogenesis of obesity and that reducing the intake of these "free" carbohydrates should be a component of efforts to control weight.

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