

The Obesity Epidemic

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The prevalence of obesity is increasing at an alarming rate and with it the occurrence of a number of comorbidities, including cardiovascular disease, type 2 diabetes, stroke, and certain types of cancer. Approximately one third of adults in the US population are currently classified as obese. Globally, $>400 \times 10^6$ adults are classified as obese, a number that is expected to double by 2015. Consequently, obesity and its associated health problems are placing a large burden on an already overwhelmed healthcare system. The worldwide costs attributable to this disease are estimated to be between 0.7% and 2.8% of total healthcare expenditures. Furthermore, medical costs for obese individuals are substantially higher than for nonobese people.

Obesity is a multifactorial disease caused by a chronic energy surplus in which energy intake exceeds energy expenditure, leading to the accumulation of excess adipose tissue. Regulation of energy homeostasis is a complex process, and that fact imparts a considerable challenge in trying to elucidate the pathogenesis of obesity. Although poor lifestyle choices, including inappropriate diets and lack of physical activity, undoubtedly play a large role, genetic susceptibility also puts an individual at increased risk.

The majority of obesity therapies have been aimed at behavior modification and pharmacologic intervention, although to date these therapies have led to only modest weight loss. Although less common, bariatric surgery has led to substantial long-term weight loss in morbidly obese patients; this type of treatment, however, is both invasive and costly.

Given the growing trend of obesity in both developed and developing countries, considerable importance has been placed on increasing awareness of the problem. In this article, 4 leaders in the field of obesity provide their opinions on obesity and discuss the latest advancements in pathogenesis, therapy, prevention, and the use of novel biomarkers to identify those at risk for future weight gain.

What are the main causes of the current obesity epidemic? Why have we not been able to combat obesity?



Arya Sharma: The current obesity epidemic is a consequence of complex factors that influence both caloric intake and expenditure. Key drivers include easy availability of energy-dense and highly palatable foods, sedentary work environments, lack of sleep, high stress levels, and increased prevalence of mental

health problems. Other factors can include epigenetic modification (in utero) related to maternal age, body composition and lifestyle, and accumulation of environmental bioactive toxins. Treatment is limited by the body's efficient ability to "protect" its weight—weight loss results in complex and persistent biological responses that promote weight regain. Thus, any approach to obesity treatment must embrace the principles of chronic disease management to prevent relapse (weight regain).



Jean-Pierre Després: It is ironic that at a time when there is so much research being conducted on the pathophysiology and management of obesity, the prevalence has never been so high worldwide. Furthermore, there is no evidence that this growing epidemic will plateau soon. Over the last 40 years, we

have learned a lot about the biological factors regulating energy balance and on the biology of adipose tissue. Thus, in theory, eating less and moving more should fix the problem.

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However, with a few rare exceptions, energy balance is largely determined by behaviors and by the quality and amount of what we eat. Thus, our energy intake/expenditure is influenced by numerous ecological, psychological, and socioeconomic factors. For instance, we know that there is an inverse relationship between socioeconomic status, level of education, level of income, and obesity. To translate this in simple terms, a single mother on welfare with poor knowledge of nutrition and little money to buy fresh fruits and vegetables will be tempted to satisfy her family with energy-dense, inexpensive, refined foods. Physical activity will be the least of her concerns, particularly if she lives in an unsafe, dangerous environment with no sidewalks or parks for her children to play safely. In addition, a whole generation of children is not being exposed to food preparation, with little nutritional education provided at school. Thus, they have no nutrition skills to cope with less-healthy nutritional offerings. Furthermore, we keep children sedentary at school, whereas we should be promoting how fun it is to “play outside” and to perform vigorous physical activity on a daily basis. The cardiorespiratory fitness of our children has never been so poor. We have to target some of the key culprit environmental factors if we want to make progress. Some pilot projects are under way, but I am not optimistic for the near future.



Shereen Ezzat: Obesity, like most metabolic disorders, is multifactorial in nature. How genetic variants interact with environmental influences will represent the focus of future research. Until then, only a very small proportion of patients with severe obesity can be genetically identified.

Our knowledge of the genesis and progression of obesity remains rudimentary.



Frank Greenway: Obesity is the result of our genetic background interacting with our environment. One can see this with the Pima Indians, who are obese in Arizona, but individuals in another tribe with the same genetic background living in rural Mexico are not obese. There are

probably multiple environmental causes of obesity including an adenovirus (Ad-36) and insufficient sleep. Thus, while obesity results from an energy surplus,

there are several genetic and environmental factors leading to that energy surplus. Once people become obese, it becomes a chronic disease in which weight is physiologically controlled at a higher-than-healthy level, similar to high cholesterol, another chronic disease that was poorly treated with diet until the advent of drugs inhibiting hydroxymethylglutaryl-CoA reductase (statins).

It is well known that there is a genetic contribution to the pathogenesis of obesity. Recently, FTO (fat mass and obesity-associated gene), located on chromosomal locus 16q12.2, was unequivocally associated with increased body mass index across a number of genomewide association studies. Are there any other robust genetic associations that have been identified? Do you believe we should start screening the general population for these polymorphisms to identify “at risk” individuals?

Arya Sharma: Twin studies show that the heritability of body composition is higher than other traits, such as blood pressure and high cholesterol concentrations. While only rare cases of obesity are attributable to monogenic disorders, there are many common variants that occur in the large number of genes (>1000) thought to be involved in key pathways in ingestive behavior and metabolism. Currently, there is no common genetic variant that would warrant genetic screening.

Jean-Pierre Després: The work on the *FTO* gene is a good example of the confusion surrounding the definition of obesity. If obesity were defined only as an excess amount of body fat with no consequences on health, it would be only a subjective cosmetic issue, similar to having a long nose or large ears. However, we are concerned about obesity due to its potentially harmful consequences for health. This is an area of considerable confusion. Obesity is a mixed bag of conditions but is unfortunately described as a single entity, which is a mistake. My work for more than 25 years has focused on one form of “obesity”: overweight and moderately obese individuals who have too much body fat stored in the wrong place (referred to as ectopic fat depots, such as excess visceral adipose tissue and liver fat). These “viscerally obese” individuals are not necessarily very obese but are at increased risk for dyslipidemias, hypertension, insulin resistance, glucose intolerance and type 2 diabetes, sleep apnea, cardiovascular disease and stroke, and some forms of cancers. Among those with an excess of visceral/ectopic fat, these complications can be observed at any level of total body fat. At the other end, there are massively obese patients who may or may not (if they do not have excess ectopic fat) be characterized by metabolic abnormalities. Irrespective of the presence/absence of metabolic abnormalities, these massively obese patients have

a deteriorated quality of life and could suffer from psychological distress and other complications due to their very high body fat content. When genomewide association studies are conducted, these 2 very different forms of obesity are not distinguished. Many experts in the field of genetics consider that the next progress in this field (now that the technology allows this type of genetic screening to be performed on a large scale) will require a more refined phenotyping of individuals. We need to go beyond simply using excess body weight or body fat as the end point.

Shereen Ezzat: It is currently premature to start screening populations for genetic polymorphisms. Until a better understanding of how such variants interact with relevant environmental factors is developed, the genetic contribution from such polymorphisms is likely to be very small. Moreover, identifying subjects with different obesity phenotypes (visceral vs global) can be readily ascertained through other modalities, such as quantitative computed tomography scanning and bioelectric impedance.

Frank Greenway: The *FTO* gene has the greatest correlation with obesity. There are other obesity-associated genes, but most account for a very small amount of the variance in body mass index. We should not screen for genetic polymorphisms associated with obesity until we understand the physiology of these associated genes so that identifying the genes will result in a better treatment for obesity. The science has not progressed to that point yet, but hopefully it will in the future.

Can you elaborate on the role of the endocrine system in the pathogenesis of obesity?

Arya Sharma: Virtually all hormones influence one or more aspects of energy intake, energy disposition, or energy expenditure. These include hormones involved in the hypothalamic–pituitary–thyroid/adrenal axis, sex hormones, catecholamines, gut hormones, insulin, glucagon, and adipokines such as leptin. All of these hormones can affect and modulate appetite, energy partitioning, and storage, as well as basal, adaptive, and activity thermogenesis. Currently, routine endocrine testing is not recommended for the diagnosis of obesity unless prompted by specific signs or symptoms suggesting an endocrine abnormality.

Jean-Pierre Després: Again, a key point in answering this question is to properly define the form of obesity that is being referred to. For massively obese patients, my opinion is that their subcutaneous adipose tissue has a remarkable, unique ability to proliferate to accommodate the increased energy flux, allowing storage of the excess energy in subcutaneous adipose tissue.

For instance, some massively obese patients have a large accumulation of subcutaneous adipose tissue without evidence of ectopic fat. In other words, their liver fat content is normal. What are the molecular mechanisms driving energy storage and promoting the expansion of subcutaneous, as opposed to visceral/ectopic, adipose tissue? This is a billion-dollar question, and numerous hypotheses are currently under study.

Shereen Ezzat: There are several derangements that occur with obesity, including increased cortisol secretion, likely driven by central/hypothalamic factors. The pituitary output of growth hormone and its peripheral target, insulin-like growth factor 1, are diminished. Moreover, increased aromatization of testosterone in fat leads to a higher estrogenic ratio, which serves to inhibit the pituitary–gonadotropin signal, further attenuating testosterone production. Finally, thyroid hormone output and diversion toward the inactive (reverse T_3) form represent an additional set of endocrine dysfunctions in obesity. It is important and necessary to distinguish downstream epiphenomena from central key effectors of obesity.

Frank Greenway: The discovery of leptin demonstrated that a hormone exists in animals and humans that causes massive obesity when absent. Those individuals with leptin deficiency respond dramatically with weight loss when leptin is replaced. Leptin has been important in convincing scientists that obesity is a physiologically controlled chronic disease that deserves study. Leptin deficiency is rare, however, and most people with obesity have high leptin concentrations. We are not sure of the pathogenesis of obesity in most people suffering from it other than to say it is an energy imbalance resulting from eating more calories than are metabolized. However, there are gut hormones such as ghrelin that increase appetite and pancreatic peptide YY_{3-36} (PYY) or glucagon-like peptide 1 that decrease appetite, and they may contribute to obesity when improperly regulated.

Leptin was identified in the mid-1990s as a novel adipokine involved in the hypothalamic regulation of satiety. Where do things currently stand with regard to this adipokine as a marker of obesity? Are there any other promising adipokines involved in appetite regulation that have recently been identified?

Arya Sharma: There are a large number of adipokines that can affect energy intake and expenditure. These include leptin, adiponectin, visfatin, and others. Cur-

rently, the measurement of these adipokines is not recommended in routine practice.

Jean-Pierre Després: The discovery of leptin was an important milestone in obesity research because it provided evidence that adipose tissue was much more than an organ specialized in the storage and mobilization of triglycerides. The spectacular response to leptin therapy in young obese children who were leptin deficient but normalized their body weight after treatment held promise. Unfortunately, it was later found that most obese patients are hyperleptinemic and that leptin concentration correlates very well with the amount of total body fat. However, a plethora of new adipose tissue cytokines (adipokines) have since been identified. At this stage, I am reluctant to focus on a specific adipokine, but this work is extremely interesting. Clearly, adipose tissue communicates with other important tissue/organ targets, such as the brain, liver, skeletal muscle, β cells, and heart, and much will be learned in the coming years.

Frank Greenway: Leptin appears to be a starvation hormone. When it is low, it stimulates appetite and decreases metabolic rate, causing obesity. Most obese people have high concentrations of leptin and insulin and are resistant to the action of both hormones. Leptin treatment seems effective only in obesity due to leptin deficiency. New adipokines are being discovered, some having effects on insulin sensitivity, but none appear to be the cure for obesity that people hoped leptin would become.

Are there any additional emerging biomarkers that have been successful in predicting those at risk of developing obesity?

Arya Sharma: Currently there are no biomarkers that will predict the development of obesity.

Jean-Pierre Després: As a result of rapidly evolving technologies, some companies offer genetic profiling and sum up the number of currently known susceptibility variants that you may have. This profiling will tell you only if you are more susceptible to put on body fat than others not having these variants. An anecdote: One colleague in academia who once had difficulties controlling his body weight told me that he requested a genetic profile and found out that he was indeed characterized by most susceptibility variants known so far. Since then, he has changed his lifestyle and has lost a considerable amount of body fat. The point is it may be harder for some genetically susceptible individuals to lose weight/body fat, but they can (in theory) better control their body weight if they acquire the skills and

knowledge to cope with their environment. The problem remains, however; if you are genetically susceptible and have many personal/professional issues to deal with because you do not have an education, your income is low, and you are struggling to survive with no skills to cope with the poor nutritional options, what can you do? We are going back to the socioeconomic, ecological, psychological drivers of unhealthy behaviors and have a long way to go to properly study and address these factors.

Shereen Ezzat: We should not forget that body composition is dependent not only on fat but on the associated loss of muscle and bone. Markers of increased loss of muscle, such as myostatin, and those of bone turnover, such as osteocalcin and type I collagen cross-link products, are likely to emerge as part of the obesity landscape.

Frank Greenway: The biomarkers that are useful in predicting obesity are distant from knowing the real physiology behind obesity pathogenesis. People who have 1 or 2 obese parents are at risk for obesity, as are those who are insulin resistant.

What are some of the treatment options currently being used to treat this disease? Are there any novel therapies in the pipeline that will become clinically available in the next few years?

Arya Sharma: At present, the most effective treatment for patients with severe obesity is bariatric surgery. In patients with moderate obesity, behavioral interventions can result in sustainable weight loss of approximately 3%–5% of initial weight. Current pharmacological options are limited, but several medications are currently under investigation.

Jean-Pierre Després: Again, one cannot address this question by considering obesity as a single homogeneous entity defined by an excess of body fat. First, the health status of the patient has to be properly evaluated. Classifying patients on the basis of their body mass index (normal weight, overweight, or obese with various classes of obesity) is a starting point but not enough. The overall health status profile of the patient is important, and a holistic approach to health must be considered. For some moderately overweight patients with excess visceral ectopic fat, the presence of comorbidities will determine health risk. For other patients, physicians should investigate the underlying possible causes of the obesity phenotypes that they evaluate in their practice. The history of the pharmacotherapy of obesity has been a series of disappointments because of the side effects of the drugs developed so far, as well as

the difficulty of targeting the right drug for the right patient. Obesity also has a cosmetic component, as opposed to other conditions such as hypertension or dyslipidemia. This is why there can be pressure on the physician from the patient to prescribe a weight loss drug that is certainly not justified if cosmetic motives are involved. With the exception of orlistat, most drugs developed so far are centrally acting with side effects making them difficult to use on a large scale. Again, to develop the right drug for the right patient remains a challenge. The recently developed approach of “metabolic surgery” also holds promise for massively obese patients and for obese patients with type 2 diabetes. Further work on this topic is clearly warranted.

Shereen Ezzat: Current therapies are mainly nonpharmacologic in nature. This is related to prior negative experiences with adverse events associated with anorexiants use. Safer anorexiants that are more targeted and selective in nature may prove worthwhile. Much more promising are agents that work on peripheral targets to enhance insulin sensitivity or promote lipolytic actions. Analogs that can activate polypeptide receptors or steroid nuclear receptors to enhance brown adipose tissue and diminish white fat differentiation may prove equally promising.

Frank Greenway: The current treatments are diet and exercise, which require people to overcome physiology with behavior, orlistat (which causes loss of calories in the stool), medications that work on the central nervous system, and surgery. Chronic disease (e.g., hypertension) treatments typically progress from surgery (e.g., sympathectomy), to drugs acting on the brain (e.g., reserpine), to combination drugs, and finally to drugs with peripheral targets (e.g., angiotensin receptor blockers). Drugs like angiotensin receptor blockers that act on peripheral targets are effective, with minimum adverse effects. Zafgen is developing beloranib, a methionine aminopeptidase 2 inhibitor in peripheral tissues, for the treatment of obesity that returns weight to wild-type levels in mice with a mutation causing leptin deficiency. Beloranib was well tolerated in an early human trial and gave 1 kg of weight loss per week over 4 weeks. If beloranib returns weight to normal with minimal side effects in humans as it did in leptin-deficient mice, it will represent a big therapeutic step forward in obesity treatment.

Although there are hundreds, if not thousands, of commercially available diets for weight loss, these

have been largely unsuccessful at maintaining weight loss. Why do you think this is?

Arya Sharma: Most commercial programs focus on maximizing weight loss, although often because of cost or intensity, they are unsustainable in the long term. These programs rarely address the underlying root causes of obesity and do not diminish the body’s biological drive to restore body weight.

Jean-Pierre Després: To be successful over the long term, patients need support to cope with the “obesogenic” environment. Long-term intervention studies have clearly shown that the greater the level and frequency of interaction between patients and the support team, the greater the likelihood that these patients will successfully maintain a reduced body weight over the long term. The billion-dollar questions are these: What kind and what level of support can we afford to offer to high-risk overweight and obese patients to help them lose some of their atherogenic and diabetogenic adipose tissue and improve their overall health profile? What kind of support team should we put in place? Should we consider a mix of personal/individualized support combined with group sessions along with electronic media interactions? Interesting pilot intervention studies have been recently published, and we need more studies on this issue. Without doubt, diet gurus publishing diet books will continue making a profit and are not the solution to the problem. We also need to target some core socioeconomic, environmental, and psychological drivers of the obesity epidemic. School is certainly a relevant epicenter to include in the “big picture.”

Shereen Ezzat: Weight loss is one process that is more easily achieved. Regain of weight likely represents a distinct set of factors, including central and peripheral signals of a somatic and neurocognitive nature.

Frank Greenway: Obesity is a chronic disease in which body weight is controlled at an increased and unhealthy level, just as blood pressure is controlled at an increased and unhealthy level in hypertension. People can overcome their physiology with behavior changes for a limited period of time, but few can overcome the physiology of a lowered metabolic rate and increased appetite that result from dieting on a chronic basis. Thus, dieting in general is almost always doomed to failure in the long term.

Denmark recently implemented a “fat tax” on all foods that exceed 2.3% saturated fat. Are you in

favor of this? Do you think a “fat tax” should be implemented globally?

Arya Sharma: Taxation has not been demonstrated to reduce the incidence or prevalence of obesity. It is also not clear that increased fat consumption is in fact a causal driver of the obesity epidemic. Indeed, given the multifactorial nature of obesity, it is unlikely that these types of measures will prove beneficial at the population level.

Jean-Pierre Després: This is a complicated issue. The quality of food is a very important driver of cardiovascular health. The American Heart Association has attempted to move away from a technical discussion on the macronutrient composition of the diet to more food-oriented recommendations. The refined-sugar content of the diet is also very important, particularly the overconsumption of sugar-sweetened beverages. We should not drink large amounts of beverages containing sugar. The fatty acid composition of processed foods is a nightmare to decipher for consumers. We need simple and clear labeling, such as “GREEN: to be consumed at every meal” to “RED: to be consumed with great moderation.” Again, this is a complicated issue, but clear labeling for the consumer along with clear food-based recommendations would be a good start for patients and consumers.

Shereen Ezzat: Tobacco and alcohol taxes have not diminished consumption of either. A higher tax burden may prove more punitive on people of lower socioeconomic status. Hence, I would not be supportive.

Frank Greenway: Nutritional epidemiologists use associations that do not imply cause and effect to drive public policy. Correlations should be hypothesis generating and call for clinical trials to confirm these hypotheses, which should then give rise to a confirmatory trial. Hypothesizing that a fat tax will have a positive effect on obesity is reasonable. Before it is incorporated into public policy, I believe that the cautious scientist would like to see confirmatory clinical trials showing that the added economic burden is justified by a positive public health outcome.

Do you have any additional comments?

Arya Sharma: It is important to view obesity as a complex multifactorial, chronic, often progressive disorder with high relapse rates. All treatments (behavioral, medication, or surgery) must be sustainable. When treatment stops, the weight virtually always comes back.

Jean-Pierre Després: Obesity, even considered as a homogeneous entity (which should not be the case), is a

marker of poor nutritional habits and lack of physical activity. Given that, we should not forget to target the underlying causes of high-risk nutritional/sedentary behaviors (psychological, ecological, economical, etc.). It cannot be emphasized enough that regular, vigorous physical activity can improve the health profile (not only metabolic variables) of almost every obese patient, even if the patient does not lose weight or a great deal of body fat. In addition, some high-risk patients will even lose quite a bit of their visceral/ectopic fat without losing a great deal of body weight. Regular physical activity has unique beneficial properties for the obese patient. In this case, the magnitude of weight loss produced by regular physical activity/exercise may not even be the best metric to evaluate its beneficial effect on patients. Regular physical activity/exercise has to be introduced to obese patients by kinesiologists, who are the professionals with the expertise to do so. They have a place in the multidisciplinary health team that should support the obese patient.

Note from moderators: The chromosome 16p11.2 locus has recently been identified as a body mass index modifier, as follows: Deletion of the locus, spanning 28 genes, increases the risk of morbid obesity by 43-fold (*Nature* 2010;463:671–5), whereas duplication of the same locus is highly associated with developmental or intellectual disabilities, including a reduced body mass index (*Nature* 2011;478:97–102). Thus, gene dosage at this region is associated with extreme body mass index phenotypes.

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