Q&A

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OBESITY

Causes and control of excess body fat

Jeffrey M. Friedman

Obesity is a major health problem in developed countries and a growing one in the developing world. It increases the risk of diabetes, heart disease, fatty liver and some forms of cancer. A better understanding of the biological basis of obesity should aid its prevention and treatment.

How is obesity diagnosed?

Obesity is defined as excessive adiposity (body fat). Because the historical method for estimating adiposity — calculating a person's buoyancy by measuring their body weight under water — is cumbersome, a surrogate measure known as the body mass index (BMI) is now routinely used. Although BMI (weight in kilograms per square of height in metres) is a convenient measure and useful for assessing the weight status of a population over time, it is often unreliable for assessing an individual's status. This is because it does not distinguish between fat and muscle mass, and the use of height squared, which, like weight, is subject to demographic shifts, is entirely empirical. Recently developed methods for directly assessing body fat, such as air displacement to calculate density, are more reliable and so should replace BMI measurements.

How big a problem is obesity?

It is a global problem. Among Caucasians, the risk of obesity-associated medical complications first becomes evident from actuarial, or mortality, tables in people with a BMI of 25 (overweight), and rises drastically in those with BMIs of 30 and above (obese). In the United States, around one-third of the population has a BMI above 30, and half have a BMI of more than 25. The aggregate economic cost of obesity in this one country is estimated to be in excess of US$60 billion per year, with a large proportion of it attributable to obesity-associated type 2 diabetes. The severity of obesity often increases dramatically when calories become freely available to populations. Hence, obesity is a growing problem in China and India, among other countries, and is likely to become a bigger problem as more nations get richer. In Asian populations, the risk of diabetes and other metabolic diseases often develops at lower BMIs than among Caucasians, amplifying the health consequences of obesity in Asia.

So is there an epidemic of obesity?

No: an epidemic typically denotes a disease that spreads from person to person and has a rapidly increasing incidence. Many trumpet a dramatic increase in the incidence of obesity, but whether this view is true depends on how one looks at the data. Variation in body weight is a continuous trait, whereas obesity is a dichotomous trait. Giving a fixed threshold to a continuous trait — for instance, that a BMI of 25 or above indicates overweight — means that a small shift in the trait's mean value leads to a disproportionate increase in the number of people who exceed the threshold. For example, there were reports in the 1990s of a 33% increase in the incidence of obesity in the United States during the previous decade, strongly supporting the role of lifestyle. What remained unreported was an average weight gain of only 3–5 kilograms over the same decade in the whole population. So the secular trend towards obesity is less profound than is generally appreciated.

Are you saying that obesity is not a disease of lifestyle?

Lifestyle or environment is probably a necessary but insufficient factor in obesity. Going back to the earlier US example, although the vast majority of individuals there have unlimited access to calories, only half of the population is overweight or obese. A key question therefore is: when provided with unlimited calories, why do only some people consume more than others, becoming obese?

And the answer is?

Although many believe that food intake is primarily a voluntary, conscious behaviour, evidence suggests that the balance between energy intake and output is largely controlled by a powerful, unconscious biological system. It stands to reason that a biological system that maintains energy balance would be under evolutionary pressure, making it weigh up the relative risks and benefits of different amounts of fat. In a hunter–gatherer society, too little fat would put an individual at risk of starvation, whereas too much of it would increase the risk of both predation and serious disease. Thus, genetic variants that contribute to leanness or obesity could both be beneficial to a population, depending on the environmental conditions. This might explain why populations that have been historically undernourished often become the most obese when suddenly provided with unlimited calories.

What about consciously balancing food intake and energy expenditure?

On the basis of the laws of thermodynamics, body weight could be controlled in this way. But the biological system that balances adipose-tissue mass resists weight change in either direction, partly by regulating the unconscious drive to eat. In the short term, therefore, a motivated individual will lose weight by reducing food intake and/or increasing energy expenditure. Eventually, however, biological factors supervene and confer a powerful, unconscious impulse to eat more until the individual returns to his or her starting weight. This is analogous to consciously holding one's breath; inevitably, the basic drive to breathe dominates the conscious motivation. Consider variations in weight among groups of individuals over time — say a year, during which an individual would consume roughly one million calories. Weight remains remarkably stable, far exceeding an individual's conscious ability to monitor their food intake and energy expenditure. A challenging question is how neural circuits that underlie the basic drive to eat interact with those that represent the conscious wish to alter one's weight.

What is the evidence for a biological basis for obesity?

Classically, a genetic contribution to a human trait is quantified by comparing the trait's variation between identical and non-identical twins. Using this approach, the heritability of obesity — percentage of variation due to genetic factors — ranges between 70% and 80%. These values exceed those for most other traits that are commonly accepted to have a biological basis, including diabetes, heart disease and cancer. Indeed, the only trait with consistently higher heritability than obesity is height. Adoption studies also support the contribution of genes to obesity: adopted children's weight more closely resembles that of their biological, rather than their adoptive, parents. Nonetheless, no study can completely attribute obesity to genes. Because no one becomes obese if they are starved, the environment — primarily, free access to calories — is probably a permissive factor that sets the stage for the genetically predisposed to become obese.

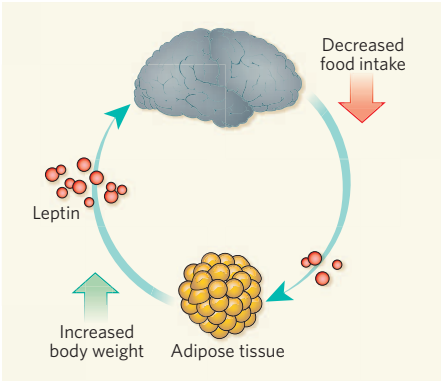

Figure 1 | Leptin and the control of body fat. With increased body weight, adipose tissue secretes higher levels of leptin. This hormone then travels to the brain, where it binds to leptin receptors in various regions, including the hypothalamus. The result is a sensation of satiety and so a decrease in food intake. Conversely a reduction in body weight lowers leptin levels and increases food intake. Thus, relative constancy of weight can be maintained.

What genes have been implicated?

Several genes, when mutated, cause obesity in humans and animals. These genes are generally components of the system that regulates energy balance. For instance, the *ob* gene encodes leptin — a hormone made in adipose tissue that acts on many physiological systems, including brain centres that control food intake and energy expenditure. With an increase or decrease in body fat, leptin levels fluctuate accordingly, leading to a respective reduction or increase in food intake (Fig. 1). Mice with mutations in *ob* fail to produce leptin and show a threefold increase in weight and a fivefold increase in body fat compared with normal mice. Humans with mutations in this gene, or in the gene for the leptin receptor, can also become massively obese. The leptin receptor is located in the hypothalamus and elsewhere in the brain, as well as in some peripheral tissues. Injury to the hypothalamus can cause obesity, partly by destroying neurons that express the leptin receptor. A class of leptin-activated neurons in the hypothalamus express the neuropeptide precursor POMC, mutations in which, or in its receptor MC4, also cause obesity.

Do only single-gene mutations cause obesity?

No. Some 5–10% of morbid obesity (BMI of 40 or more) is due to defects in the above genes and in other genes that function in the brain circuits, including that encoding the neuropeptide BDNF. This is an unusually high frequency for the Mendelian inheritance of a complex trait. In the rest of the population, however, a combination of genes and their interaction with the environment is thought to cause weight variation. Several genes that affect weight have been identified through genome-wide association studies. One such gene is *FTO*, the function of which is unknown, but DNA-sequence variations in it can account for a 3–5-kilogram weight difference. The fraction of genes such as *FTO* that have been shown to contribute to obesity in the general population is relatively low. So it remains unclear whether such genes contribute to obesity through many different single-gene mutations or through potentially complex interactions involving several genes, each having small effects on their own (or a combination of both).

Is there a difference in the metabolism of lean and obese people?

Not if one measures only lean body mass. But when obese people lose weight, their energy expenditure is reduced disproportionately to their change in weight. These 'reduced obese' people use less energy than lean individuals of that weight who have not been obese. And to maintain their reduced weight, they must consume fewer calories than their initially lean counterparts. This disadvantage in itself undoubtedly contributes to the high rate of recidivism after dieting, especially as it occurs at a time when the basic drive to eat is activated by reduced leptin levels.

What hormones, other than leptin, are involved?

Whereas leptin maintains constant energy stores over long periods, there's another system that maintains relatively constant levels of nutrients in the blood in the short term, for instance throughout the day. This system, which controls both hunger and satiety, consists of many blood-borne and neural signals. The blood-borne signals include metabolites — such as glucose, and possibly amino acids and fatty acids — and hormones of the digestive system, including the stomach hormone ghrelin and intestinal peptides such as GLP-1, peptide YY, cholecystokinin, bombesin and amylin. These short-term signals act on neurons in the brainstem and hypothalamus to regulate both food intake and the intervals between meals. The short- and long-term systems interact extensively.

So it seems that several tissues and organs regulate weight?

Indeed. Food intake and body weight are controlled by an intercalated feedback loop. Signals from numerous tissues that together form the short- and long-term systems — including adipose tissue and the gut — travel to integratory brain centres, where they are decoded. The neural pathways then control food intake and metabolism in several

peripheral tissues (Fig. 2). Although substantial progress has been made in defining the neural pathways that control food intake, less is known about the circuits that regulate energy expenditure, and fat and glucose metabolism.

If predisposition to obesity is determined by our genes and metabolism, why diet or exercise?

Weight loss alleviates obesity-associated medical complications, with even modest losses of 5–7 kilograms having disproportionate benefits to health. Many people can achieve this amount of weight loss, partly because the potency of the biological factors that resist changes in weight is greatest after larger amounts have been lost. So my advice to obese individuals is the same as I would offer anyone: do what you can to improve your health. Eat a heart-healthy diet, begin a programme of physical activity, and try to lose as much weight as is required to improve your health, without feeling compelled to 'normalize' your weight.

Can gut microorganisms cause obesity?

Some studies have suggested a small but significant contribution of the gut microbiota, although the underlying mechanism is unknown. The contribution of such organisms, however, seems to be much smaller than that of the host genes. In animals, certain viruses can cause obesity by damaging the hypothalamus, but this effect has not been seen in humans.

Does the cause of obesity affect its severity?

Demonstrably so among those with specific obesity-related mutations. Patients with mutations in leptin or in the leptin receptor, for example, are more obese than those with mutations in POMC, MC4 or BDNF. Among obese people in the general population, there is probably a similar or even greater degree of variation. To identify such differences, respective genetic determinants in subgroups of obese people must be identified — an endeavour that is already under way.

What anti-obesity therapies are out there, and how effective are they?

One effective therapy is bariatric surgery to modify the anatomy of the gastrointestinal tract, thereby reducing food intake and/or absorption. Because all bariatric procedures can potentially cause serious morbidity and even death, this treatment is typically reserved for those with severe medical problems. Besides, even after surgery, most patients remain clinically obese (BMI more than 30), despite the marked reduction in their food intake. This fact highlights the biological difference between the morbidly obese and individuals of average weight. The reason for the effectiveness of bariatric surgery is unclear.

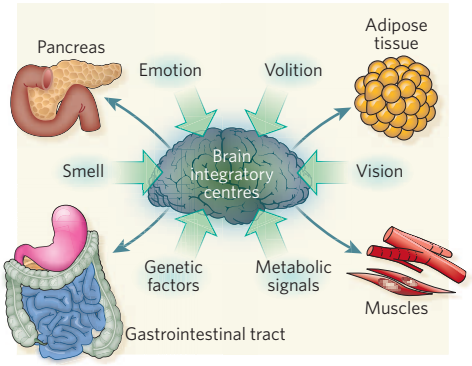

Figure 2 | Feeding is a complex, motivational behaviour. Several behavioural, genetic and metabolic signals regulate feeding through signals that travel from distinct peripheral tissues to integratory centres in the brain. After processing these signals, the brain modifies feeding and also sends appropriate commands to specific peripheral tissues to regulate metabolism.

Many believe that its benefits are primarily due to alterations in neural, metabolic and hormonal signals from the gastrointestinal tract to the brain, rather than a mechanical alteration that physically limits food intake. A major goal is to identify the specific signals that are altered by this procedure. The alternative procedure of liposuction is effective only in the short term, as the lost fat is eventually regained, probably because leptin levels are lowered after the removal of large amounts of fat, and so food intake increases. Leptin-replacement therapy in those deficient in this hormone is another approach that results in dramatic weight loss in animals and in the small number of humans with leptin mutations; to date, there are no known disadvantages of this treatment.

What are the hottest developments in obesity research?

For one, our increasing ability to identify specific neural pathways that control feeding and to assess how modulating the activity of such neurons affects feeding behaviour. For instance, manipulation with light, involving the light-activated ion channel known as channel rhodopsin, can be used to examine the effect of activating or inhibiting a neuron. Also, functional imaging has recently been used to map the human brain regions that control eating. Such studies have revealed leptin-mediated changes in neural circuits that control reward-associated behaviour, providing a link between neurobiology and psychology. As for research into anti-obesity therapy, emerging data show that leptin and amylin together produce a potent signal to induce substantial weight loss. The aim now is to evaluate the safety and long-term efficacy of this combined therapy.

And what are the most pertinent remaining questions?

A crucial objective is to understand the way in which diverse inputs lead to a single behavioural response — feeding. We do not know how this complex information is represented in the brain centres that control eating, or even where exactly these centres are. Answers to these questions may eventually reveal how and why, at a neurobiological level, the conscious desire to lose weight is so often dominated by the basic drive to eat. Another outstanding goal is to identify all of the genetic variants that contribute to differences in weight.

What might the future hold?

When there is no appreciable risk of starvation, obesity simply leads to disease, and so evolution should select against it. Indeed, on the Pacific island of Nauru, a profound increase in the incidence of diabetes after the introduction of a high-calorie diet was followed by a decrease, suggesting that there was evolutionary selection against diabetes when the incidence became very high. There is also evidence from the United States that the incidence of obesity may be reaching a plateau. I therefore anticipate that body weight will stabilize in the population over the coming decades.

So is taking action justified?

Regardless of future trends, developing effective and safe anti-obesity therapies is essential and feasible. I consider it less likely that drugs to normalize the weight of morbidly obese people will be developed any time soon; and anyway, whether such drugs would bring added health benefits is unclear. The focus should be on designing treatments that can stably maintain moderate weight loss, improving an individual's health. With the growing realization that mainly biological factors contribute to obesity, it is hoped that this condition will be de-stigmatized, reducing the compulsion by obese individuals to achieve an (arbitrary) ideal, lean weight and instead motivating them to focus on improving their health. This outcome will best serve our larger interests and reflect better on all of us. ■

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The author declares competing financial interests. See online article for details.

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