

## In Brief

Understanding the physiology behind the regulation of body weight can help clinicians treat and educate obese patients. This article reviews the current knowledge of body weight regulation and the metabolic changes that occur in the body in response to weight loss. The physiological basis for the difficult nature of weight loss, and especially maintenance of lost weight, is discussed.

# The Physiology of Body Weight Regulation: Are We Too Efficient for Our Own Good?

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A constellation of clinical studies has established the close link between obesity and type 2 diabetes.<sup>1-3</sup> This correlation, however, is not perfect; many diabetic patients are not obese, and many obese individuals are perfectly responsive to insulin. Regardless of whether a causal relationship exists between obesity and the body's response to insulin, beneficial effects of weight loss on the metabolic parameters of many diabetic patients are well documented.<sup>4-6</sup> Thus, it is not surprising that a combination of weight loss and exercise is an effective treatment for many diabetic patients.<sup>7</sup>

Both the American Diabetes Association and the National Institutes of Health have recommended that health care professionals advise obese diabetic patients to lose weight.<sup>8,9</sup> However, while losing weight in the short term is achievable, maintaining reduced body weight over the long term has proven to be exceedingly difficult for most people.<sup>10,11</sup> At least part of the reason behind the difficulty of maintaining a reduced body weight is the body's ability to activate adaptive mechanisms that act to minimize weight loss.

The purpose of this article is to describe the physiological basis of body weight maintenance and the metabolic changes that occur in the body in response to weight loss. Understanding the inherent difficulties associated with maintaining long-term weight loss may allow patients and those with the responsibility of managing their diseases to appreciate the obstacles. This article does not

minimize the role of personal will and commitment in achieving long-term weight loss by emphasizing the role of physiology and genetics. In contrast, combined with the message that long-term weight loss is difficult but achievable, a realistic assessment and acknowledgement of the contribution of genetics in weight maintenance may help to overcome the perception that obesity is exclusively caused by over-indulgence. A deeper understanding of the complex nature of body weight regulation may induce more individuals to become committed to making lasting lifestyle changes to achieve and maintain a healthy weight.

### Evolution and an Organism's Ability to Maintain Body Weight

Body weight is determined by energy intake on one hand and energy expenditure on the other. Imbalance between energy intake and expenditure results in a change in body weight. Organisms expend energy to perform daily work required for survival, such as finding food or evading predators. Metabolic efficiency refers to the amount of energy an organism has to exert to perform a given amount of work.

Metabolic efficiency varies among different species of organisms and among different individuals within a species. An individual with high metabolic efficiency will expend less energy to perform a specific task, such as climbing a set of stairs, than an individual with low metabolic efficiency. Compared with an individual with low metabolic efficiency,

an individual with high metabolic efficiency is better able to preserve body weight during negative daily energy balance (expenditure exceeding intake), but likely to gain more weight during positive energy balance (intake exceeding expenditure). The ability of an organism to minimize reduction in body weight during long periods of starvation is likely associated with its survival. As a result, millions of years of evolution may have favored organisms with high metabolic efficiency.<sup>12-15</sup>

Organisms are very adept at acquiring and storing energy. Most of vertebrates' energy reserve exists in the form of fat. One pound of fat contains more energy than one pound of dynamite. Complicating matters is the fact that we gravitate toward our food sources. It would be much easier to achieve and maintain weight loss if we treated our daily sustenance with the same disgust as we do cough syrup. In fact, it's just the opposite; foods with high energy density, such as sugar and fat, tend to be more palatable.<sup>16</sup> Perhaps the human association of eating with pleasure may have an evolutionary origin similar to our aversion to the bitter taste of toxic plant compounds.<sup>17</sup>

### Genetic Contribution to Metabolic Efficiency and Regulation of Body Weight

Lifestyle (sedentary or active) has a clear influence on body weight. The rapid rise in the incidence of obesity in recent decades, with the percentage of overweight or obese adults reaching 66% in the United States according to the Centers for Disease Control and Prevention, cannot be attributed to genetics alone. However, results of many studies indicate that genetic factors do play an important role.<sup>18</sup> In rare cases, obesity has been traced to mutations in single genes.<sup>19</sup> Usually, these genes code for proteins involved in the regulation of satiety and food intake, such as leptin (Ob), the leptin receptor (Ob-R), pro-opiomelanocortin (POMC), and the melanocortin 4 receptor (MC4R).<sup>20</sup> Although these mutations have so far been attributed to only a few isolated families, the observation that virtually all of the affected genes play a role in the neuronal control of satiety suggest food intake rather than metabolic efficiency as a prime driver in body weight regulation.<sup>20</sup>

Many different types of studies have demonstrated the importance of genetic factors in the maintenance of body weight, and detailed reviews are available.<sup>21,22</sup> Just a few of these studies are described here. To assess the relative contribution of genetics and family environment to body weight in the wider population, a study was conducted two decades ago in Denmark comparing the BMI of > 500 adoptees with that of their biological and adoptive parents.<sup>23</sup> Although there was a positive correlation in BMI between the adoptees and their biological parents, no relationship was found between adoptees and their adoptive parents.

Metabolic studies of monozygotic twins have also provided compelling evidence for the role of genetics in determining body weight. One study examined the effects of overfeeding on weight gain in pairs of monozygotic twins.<sup>24</sup> Although all of the individuals in the study consumed the same amount of calories for the same amount of time (approximately 3 months), there was a large variation in the degree of weight gain, from 8.8 to 29.3 lb, among different individuals. However, the amount of weight gain was very similar within each twin pair. The reverse also holds true. When moderately obese monozygotic twins were kept on a low-calorie diet, the amount of weight loss varied greatly among different pairs of twins.<sup>25</sup> However, within each pair of twins, the amount of weight loss was quite similar. These results indicate that the body's response to changes in caloric intake is dictated at least in part by genetics.

Another line of evidence supporting the role of genetics in body weight regulation came from comparison of metabolic differences in individuals belonging to different ethnicities. In one study, a group of overweight women (average BMI ~ 29 kg/m<sup>2</sup>) were kept on a low-calorie diet for a period of time until their BMI decreased to < 25 kg/m<sup>2</sup>, the defined upper range of what is considered normal weight.<sup>26</sup> When these age-, weight-, and BMI-matched women were separated based on ethnicity (in this case African-American or white), differences in resting energy expenditure were apparent before and after weight loss. Although this study involved only a limited number of subjects, the results nevertheless suggest

that individuals belonging to different ethnic groups differ in metabolic efficiency; those with lower energy expenditure while maintaining the same body weight are more efficient and therefore more prone to weight gain. Interestingly, African-American women had larger decreases in resting energy expenditure after weight loss, suggesting that they may be at higher risk to regain the lost weight. In addition, children belonging to different ethnicities also have different resting energy expenditures.<sup>27</sup>

### Control of Body Weight at the Molecular Level

Body weight regulation and energy homeostasis is controlled by a myriad of metabolic pathway intermediates and endocrine control systems. Food intake is under the control of the central nervous system through many interconnected neuroendocrine and neurotransmitter circuits.<sup>28</sup> Energy expenditure is regulated by the autonomic nervous system and numerous endocrine hormones, the most prominent of which are the thyroid hormone system.<sup>11,29</sup> It is beyond the scope of this review to describe any of these control systems in sufficient detail. Instead, we will focus on one endocrine hormone with particular relevance to patients with type 2 diabetes: insulin.

Insulin likely predates leptin as an ancestral energy homeostasis hormone. Insulin and insulin-like growth factor 1 (IGF-1) signaling systems are involved in the regulation of life span, reproductive maturity, and body size in the nematode *Caenorhabditis elegans* and the fly *Drosophila melanogaster*, two organisms that do not have leptin.<sup>30</sup> In vertebrates, insulin regulates energy homeostasis and body weight through both the central nervous system and through its effects on lipid and glucose metabolism.<sup>31,32</sup>

In healthy individuals, insulin levels rise after a meal. Insulin readily crosses the blood-brain barrier<sup>33</sup> to enter the central nervous system and bind to receptors located in the hypothalamus, the area of the brain that controls feeding behavior and energy homeostasis.<sup>33</sup> Insulin is known to inhibit food intake by decreasing the expression of the orexigenic neurotransmitter neuropeptide Y.<sup>32</sup> These scientific findings are in contrast to a number of recent popular nutrition recommendations that suggest the

rise in endogenous plasma insulin during the postprandial period is correlated with an increase in subsequent appetite. This hypothesis has been studied by a number of investigators, in lean<sup>34</sup> as well as obese<sup>35</sup> humans. In general, the results of these studies do not support a direct role of insulin as an appetite stimulant in humans.

Insulin has profound metabolic effects in the determination of body weight that are independent of its neuroendocrine action in the central nervous system. Insulin is an anabolic hormone that promotes storage of glucose and fat. Weight loss is often seen in diabetic patients with poorly controlled blood glucose because of a near complete lack of insulin. Without insulin to inhibit hormone-sensitive lipase, internal adipocyte triglyceride stores are hydrolyzed to fatty acids and glycerol and released into the circulation, causing the blood to become lipemic and take on a cloudy appearance. In diabetic patients lacking insulin, body weight is reduced as triglyceride stores become depleted.

An opposite phenomenon often occurs in patients taking the thiazolidinedione (TZD) class of insulin sensitizers. This class of peroxisome proliferator-activator receptor- $\gamma$  (PPAR- $\gamma$ ) agonist drugs include pioglitazone and rosiglitazone. One of the common side effects of these drugs is weight gain resulting from expansion of adipose tissue.<sup>36</sup> This effect is likely associated with the well-documented effect of PPAR- $\gamma$  activation in inducing adipocyte differentiation.<sup>37</sup> In obese and insulin-resistant Zucker rats, administration of a TZD compound led to decreased plasma glucose, insulin, and triglyceride levels that were associated with a fourfold increase in the number of small adipocytes.<sup>38</sup>

Thus, it appears that the insulin-sensitizing effect of TZD treatment is closely tied to the expansion of adipose tissue and weight gain. Indeed, it has been proposed that insulin resistance and type 2 diabetes is, in part, caused by the inability of adipose tissue to expand.<sup>39</sup> High levels of circulating free fatty acids and triglyceride content in liver and muscle have all been linked to the development of insulin resistance.<sup>40,41</sup> The mechanism by which adipose tissue expansion improves whole body insulin action is thought to be twofold: 1) triglycerides in liver and muscle and circulating free fatty acids are transferred and

sequestered in adipose tissue where they can be properly stored, and 2) those adipocyte hormones with insulin-sensitizing effects are restored to normal levels.<sup>42</sup>

The close association between insulin sensitivity and adipose tissue expansion reflects the fact that improved insulin responsiveness in adipose tissue, the “culprit” behind increased fat deposition in adipose tissue, is coupled to enhanced insulin action in muscle and liver. The connection between insulin action and body weight has in fact led to the proposal that insulin resistance develops as an adaptive physiological mechanism to prevent additional weight gain.<sup>43</sup> As described earlier, evolution may have selected for organisms that are metabolically efficient and can buffer reduction in their body weight. However, there is an equally good argument for evolution to select for organisms that can prevent their body size from becoming too large. An oversized organism may have difficulty catching prey or evading predators. Organisms that have evolved a regulatory system to maintain a set weight may have a selective advantage. Decreased responsiveness to insulin in adipose tissue will lead to a propensity to reduce fat deposition, resulting in elevated fatty acid levels and triglyceride content in muscle and liver, and whole body insulin resistance. This situation essentially allows an organism to buy extra time, avoiding imminent demise at the mouth of a predator but risking diabetes and its complications in the future years.

The possibility of insulin resistance being tied to the prevention of additional weight gain holds serious implications for therapeutic modalities aimed at improving insulin action in type 2 diabetic patients. If the hypothesis stated above is true, it may be next to impossible to separate weight gain from improving insulin sensitivity in the absence of a persistent and aggressive exercise regimen.

### Physiological Basis for Difficulty to Lose Weight

It is well documented that, although most people participating in weight-loss programs can successfully lose weight in the short term, the majority of them cannot sustain the reduced body weight in the long run.<sup>10,11</sup> A plausible hypothesis that can account for the body's tendency to return to its

prior weight can be stated as follows: body weight is maintained at a set level, and deviations from the preferred set point are resisted and minimized by a feedback control system.

This so-called set-point theory of body weight regulation has been slowly developed over a number of years and backed by a plethora of experimental approaches.<sup>11,44</sup> First, many species of mammals, including humans, whose body weights were altered by overnutrition or undernutrition will eventually return to their original weight once the normal feeding pattern is resumed.<sup>45</sup> Second, lesions in the ventromedial hypothalamus of rodents caused by gold thioglucose administration or surgery led to overfeeding and obesity.<sup>46</sup> These experiments established an anatomical location of one hypothetical regulatory feedback mechanism predicted by the set-point theory. Third, parabiosis experiments in which the circulatory system of a normal or an *ob/ob* mouse was allowed to slowly exchange with that of a *db/db* mouse demonstrated the presence of a soluble, circulating factor that can inhibit feeding.<sup>47,48</sup> In these experiments, abnormally high levels of leptin are produced from the *db/db* mouse, which lacks the receptor for leptin. The leptin then travels through the parabiotic junction into either an *ob/ob* or a normal mouse. Having functional receptors for the high levels of leptin coming from the *db/db* mouse, the *ob/ob* or the normal parabiotic pair soon stops eating and dies within a month from starvation. These experiments demonstrated the existence of a molecule that can act as a signal in the weight-maintaining feedback control system.

These early experiments predicted the role of leptin and its receptor as one feedback control loop that regulates body weight in rodents.<sup>49</sup> Produced by adipocytes, leptin levels rise or fall depending on the size of the adipose depot.<sup>49</sup> When the size of the adipose depot is sufficient, elevated levels of leptin travel to the ventromedial hypothalamus, where the leptin receptor is rather abundant, and initiates a series of events that result in aversion to feeding.<sup>50</sup>

In addition to food intake, leptin plays a permissive role in the immune response and reproduction.<sup>51</sup> Although the leptin signaling system can dictate body weight in rodents, its significance in regulating body weight in humans

remains unclear. Obese humans already have high levels of leptin; they are refractory to the effects of leptin, a condition called “leptin resistant.” In fact, one study in obese rats demonstrated that the anorexic and subsequent weight loss effects of metformin may be related to the amelioration of leptin resistance in the hypothalamus.<sup>52</sup> It is unclear whether metformin treatment improves leptin sensitivity in humans. In any case, with the discovery of additional signaling systems that can fulfill the functional requirement of the feedback control loop, we now understand that leptin is just one of many systems capable of influencing body weight.

Although we are getting an ever-clearer picture of the feedback control mechanisms predicted by the set-point theory at a molecular level, it is necessary to measure energy intake and expenditure before and after weight change to understand why long-term changes in body weight are difficult to maintain. In 1995, Leibel et al.<sup>53</sup> conducted a study that examined energy expenditure in healthy nonobese and obese volunteers who either gained or lost 10% of their initial body weight through over- or underfeeding. After a 10% weight gain, total energy expenditure increased as expected. However, the magnitude of the increase in energy expenditure was more than what was expected based on the 10% increase in body weight. Interestingly, resting energy expenditure did not change much for either the nonobese or the obese group. It was an increase in the nonresting energy expenditure that accounted for most of the difference in total energy expenditure. A major component of nonresting energy expenditure is accounted for by skeletal muscle. Increased nonresting energy expenditure in the absence of increased activity (a value that normally varies but was kept constant in this study) suggests that, after weight gain, muscle expends more energy to accomplish the same task.<sup>53,54</sup> It becomes less metabolically efficient. This has the effect of buffering against further weight gain.

In contrast to weight gain, a 10% weight loss resulted in decreased energy expenditure beyond what was expected of a 10% loss in body weight.<sup>53</sup> Also different from weight gain, both resting and nonresting energy expenditure decreased after weight loss. With the 10% loss, the

body is now more metabolically efficient, requiring less energy than before at rest, as well as expending less energy during exercise. This projects against additional weight loss.

This finding can explain many people’s experience of not being able to lose the “last few pounds” of a set weight-loss goal. It can also provide a potential explanation for why it is relatively effortless to gain lost weight back. With the body being more metabolically efficient than before, a return to the original feeding level after a period of weight loss through decreased caloric intake would regain the lost weight. For individuals who are particularly efficient, it may even lead to net weight gain.

It is unclear at present how long the larger-than-expected decrease in energy expenditure will persist after weight loss. Perhaps the body will eventually adjust to the new weight, and it will be easier to maintain the reduced weight. Indeed, some investigators have reported that, in sustained weight loss, changes in energy expenditure eventually stabilized and were not larger than expected.<sup>55,56</sup>

In addition to decreasing energy expenditure, weight loss is also associated with an increase in appetite.<sup>57</sup> Doucet et al.<sup>58</sup> reported that subjects who successfully underwent a weight-loss program consisting of energy restriction plus exercise reported an increase in the fasting desire to eat, as well as a more intense feeling of hunger, coupled with greater food consumption. The increased hunger in these subjects was associated with higher levels of fasting cortisol.

Diet-induced weight loss is also associated with increased basal and postprandial ghrelin levels.<sup>59</sup> Ghrelin is an orexigenic hormone that is secreted primarily by the stomach and duodenum.<sup>60</sup> Normally, ghrelin levels rise before meals (associated with the urge to eat) and are suppressed after eating.<sup>61</sup> In addition to appetite stimulation, the administration of exogenous ghrelin is associated with a decrease in metabolic rate<sup>62</sup> and fat catabolism.<sup>63</sup> Thus, higher levels of ghrelin after weight loss promote weight regain by two mechanisms: an increase in energy intake combined with a decrease in energy expenditure.

In summary, regulation of body weight involves complex signaling systems and compensatory changes in appetite and metabolic efficiency. Cur-

rent evidence points to the existence of a set point that makes weight loss or gain progressively difficult. However, as with most biological systems, there is likely to be an upper and a lower limit for how much metabolic efficiency can change. As long as energy expenditure exceeds that of intake, a decrease in body weight must occur. That can be stated with absolute certainty.

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