Leptin and Adiponectin: Examining Their Clinical Significance in Obesity

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Abstract
This brief review describes the biological roles of the adipocytokines leptin and adiponectin, and examines their clinical significance in relation to obesity and obesity-related disease.

Leptin and adiponectin are adipocytokines (adipocyte-derived secreted proteins) that play a role in obesity and insulin sensitivity. Disturbances of these hormones have been associated with rare genetic obesity and lipodystrophy disorders, and are thought to have downstream effects on insulin signalling and the risk of type 2 diabetes (T2D) in these disorders. Nonetheless, alterations in leptin and adiponectin are not thought to be the primary drivers of common obesity.

Leptin was first isolated in mice through positional cloning of the mutated ob allele that conferred the obese trait on mice that were homozygous for it. These “ob/ob” mice were obese and hyperphagic from a young age, and were also infertile. Shortly after the cloning of the leptin gene in mice, human beings with congenital leptin deficiency were reported to have a similar hyperphagic phenotype, proof that leptin was also important in human energy balance. Leptin is secreted into the circulation by adipocytes, more or less in proportion to the amount of body fat. One of its actions is to signal the hypothalamus and brainstem to the state of the body’s adipose tissue reserves, so that the organism can better regulate energy intake and expenditure. Under certain circumstances, high levels of leptin can suppress food intake, but its main physiological role seems to be as a signal of low circulating leptin levels signals the hypothalamus to increase food intake and become obese.

The true effect of leptin on energy expenditure is controversial; leptin replacement given in the context of congenital leptin deficiency in mice and humans results in slightly increased energy expenditure, though these increases were calculated relative to a baseline state of dramatically reduced energy expenditure (as might be expected in an organism that perceived starvation). Leptin supplementation to adults with common, complex obesity did not increase energy expenditure compared to non-obese adults, and leptin replacement given to lipodystrophic individuals who have a functional leptin deficiency (due to a lack of fully-differentiated adipose tissue) actually reduced their energy expenditure, possibly by reducing lipid-mediated inflammation in multiple nonadipose tissues.

Leptin deficiency is a cause of obesity, and studies show leptin replacement therapy can cause weight loss and correct metabolic abnormalities in these rare individuals. However, most obese individuals have elevated levels of leptin that is made by their own fat cells. Though initially there was great optimism that leptin would be a breakthrough drug for weight loss, clinical trials showed that exogenously administered leptin has very modest effects on weight in normal humans with polygenic/multifactorial obesity. The lack of clinical efficacy may be a result of leptin resistance (perhaps due to saturation of leptin receptor-mediated transport across the blood-brain barrier). Though the exact molecular mechanism remains unclear, what is clear is that leptin confers metabolic benefits when given to leptin-deficient individuals, but “topping up” people who already have lots of leptin has minimal benefits.

Circulating leptin levels do not change acutely following a meal, but they do decrease after longer term fasting (12-72 hours). That physiological decrease in leptin levels signals the body to conserve energy through multiple pathways, including...
reductions in the levels of thyroid hormone and reproductive hormones. Interestingly, a complete loss of leptin, such as in congenital leptin deficiency, leads to central hypogonadism and failure of pubertal development. Administering recombinant leptin to those with congenital leptin deficiency results in normal pubertal onset. In other medical conditions wherein low leptin levels are attributable to a lack of subcutaneous fat (such as congenital lipodystrophy or HIV lipodystrophy), leptin treatment has restored reproductive function, improved hepatic insulin sensitivity and glycemic control, and normalized triglyceride levels. Among women with centrally-mediated amenorrhea, treatment with leptin restores menstrual cycling, normalizes reproductive hormone levels, and facilitates ovarian follicular development. Taken together, the data above strongly imply that leptin’s major metabolic effects are on food intake and insulin sensitivity, rather than on energy expenditure.

Another important adipocytokine is adiponectin, encoded by the ADIPOQ gene, which was identified in 1995 and was shown to possess anti-diabetic and antiatherogenic properties. Though it was at first thought to be made only by adipocytes, it has subsequently been shown to be secreted by the placenta. Adiponectin circulates as a multimeric complex, with high-molecular weight (HMW), medium-molecular weight (MMW) and low-molecular weight (LMW) complexes observed. Disentangling the specific effects of each of these complexes has proven to be challenging. However, levels of the HMW form correlate more strongly with aspects of the metabolic syndrome than do levels of the MMW or LMW forms. Higher levels of HMW adiponectin are associated with greater fat oxidation, a higher glucose disposal rate, and a lower central fat distribution. Powerful genetic evidence for this assertion comes from the fact that a mutation in ADIPOQ that interferes with the assembly of high-molecular-weight multimers is a strong risk factor for metabolic syndrome.

Adiponectin acts through two primary adiponectin receptors, AdipoR1 and AdipoR2, that are chiefly expressed in skeletal muscle and liver. AdipoR1 activates AMP-activated Kinase (AMPK), and AdipoR2 activates peroxisome proliferator-activated receptor alpha (PPARα), two important regulators of lipid and glucose metabolism that also modulate insulin sensitivity. Adiponectin appears to play an important role in obesity-linked diseases such as insulin resistance and type 2 diabetes. Infusions of adiponectin into the brains of mice have been shown to reduce visceral fat by increasing energy expenditure, as well as by increasing peripheral insulin sensitivity.

Mice lacking adiponectin display moderate insulin resistance and glucose intolerance. As expected, mice lacking adiponectin receptors show a similar phenotype. When placed on a high-fat diet, transgenic mice that over-express adiponectin (gAd Tg mice) gain less weight and accumulate less fat than do wild-type (WT) mice on the same diet. When placed instead on a low-fat diet, mice over-expressing adiponectin live longer than WT mice and also manifest increased hepatic insulin sensitivity. When ob/ob mice (mice with no leptin) are bred to these transgenic adiponectin overexpressors, the resulting gAd Tg ob/ob mice have better insulin sensitivity and an increased expression of molecules involved in fatty acid oxidation, relative to their littermates than do ob/ob mice without the transgene. Furthermore, these gAd Tg ob/ob mice showed an amelioration of diabetes, despite being just as obese as ob/ob mice. Thus, proper functioning of adiponectin and its receptors is important in regulating insulin sensitivity (glucose uptake) and fatty acid oxidation (energy consumption).

Rare human mutations in ADIPOQ have been shown to correlate with aspects of the metabolic syndrome. One mutation that causes premature termination results in significantly lower levels of adiponectin, and T2D by the age of thirty. Another, which impairs the formation of HMW adiponectin, also results in lower levels of adiponectin, as well as T2D by the age of thirty-four.

In contrast to circulating leptin levels, which increase as fat mass increases, circulating adiponectin levels vary reciprocally with fat mass. In other words, the thinner someone is, the more adiponectin their fat cells make. Adiponectin increases whole-body insulin sensitivity, such that a homeostatic feedback loop becomes an emergent property of the fact that adiponectin levels vary reciprocally with fat mass. When fat stores are low, as in anorexia nervosa, fat cells make copious amounts of adiponectin to increase insulin sensitivity, thereby readying the body to store fat once calories become available. The above-cited experiments in adiponectin over-expressing mice have shown that adiponectin has effects on adipose tissue itself (at least in a developmental gain-of-function paradigm). Although they also became obese, these transgenic ob/ob mice show smaller, seemingly healthier adipose cells, lowered serum triglyceride levels and normalized glucose and insulin levels compared to the obese ob/ob mice. Genes associated with lipid oxidation were also up-regulated in these transgenic mice. It seems, then, that this adipocytokine regulates insulin sensitivity to some extent through specific endocrine, paracrine or autocrine effects on adipose tissue itself. Conversely, when fat stores in humans are excessive, adipocytes make lower amounts of adiponectin, insulin sensitivity of fat cells decreases, and calories are then shunted to nonadipose tissues such as liver and muscle. This would not be detrimental if the calories were then stored safely or burned by those tissues, but if they lead to ectopic fat accumulation then the insulin sensitivity of those tissues would also decrease, potentially leading to a decrease in whole-body insulin sensitivity.

Adiponectin measurements on their own have not proven clinically useful and are still confined to the research sphere. However, serum leptin levels may be diagnostically useful in specific situations. When patients present with a clear phenotype associated with congenital leptin deficiency, such as true hyperphagia without features of other hyperphagic conditions (such as Prader-Willi syndrome), leptin levels can inform patient management. In patients with lipodystrophy or hypothalamic amenorrhea, measurement of leptin levels may also be useful because exogenous leptin (still an investigational drug) has been shown to improve insulin sensitivity and the metabolic profile. Because both leptin and adiponectin are markers of fat mass and insulin resistance, it has been proposed that the ratio of leptin to adiponectin could be used as an indication of insu-
lip resistance. The leptin-to-adiponectin ratio (LAR) correlates significantly with measures of fasting insulin, HOMA-derived insulin sensitivity, and insulin resistance as determined through hyperinsulinaemic–euglycaemic clamp studies. Because LAR can be measured in the non-fasted state, it may be more convenient surrogate measure of insulin sensitivity than HOMA-derived insulin sensitivity. However, validation of the LAR across multiple populations to determine the reference ranges has yet to be done.

It is important for physicians to be aware of the effects of leptin and adiponectin as research on these two adipocytokines continues. Though they have not yet been validated fully for clinical use in polygenic/multifactorial obesity, when leptin and adiponectin are assayed and interpreted in the context of the patient’s fat mass, the two hormones can give a physician a clearer picture of the physiological (or pathophysiological) functioning of the adipose tissue in patients with rare forms of obesity and lipodystrophy. Thus, they could be used to supplement clinical suspicion of a rare disorder when other indications (such as an unusual metabolic profile or an unusual distribution of visceral and subcutaneous fat) are present.

References