Leptin and insulin resistance: good, bad, or still unclear?

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TO THE EDITOR: the article by Paz-Filho et al. (13) addresses the potential changes in insulin sensitivity in patients with congenital leptin deficiency while on leptin therapy and off leptin therapy. Using the hyperinsulinemic euglycemic clamp technique, the investigators showed an increase in whole body glucose disposal during a period of leptin withdrawal compared with a period of active therapy for 3 subsequent yr. Although only three patients were studied, investigation of the insulin sensitivity in this unique group of patients is an important addition to the literature since detailed investigation of insulin sensitivity in patients with congenital leptin deficiency has not been reported previously (2–4, 8, 9, 12). However, we urge caution in the interpretation of results.

The studies off of leptin occurred at a time when weight was not at steady state; subjects were rapidly gaining weight at the time of the study. As pointed out by these authors, this makes the interpretation for a direct role for leptin in insulin resistance difficult. Previous studies reported increased insulin sensitivity during times of weight regain (15). Improved insulin sensitivity is thought to predict future weight regain in subjects at the end of weight reduction programs. We believe that the study by Paz-Filho et al. (13) actually provides further evidence that rapidly expanding adipose tissue improves whole body insulin sensitivity, at least at short term.

The exact mechanisms (such as regulatory signals) leading to slightly improved insulin sensitivity at initiation or during weight regain are not well understood. A simple explanation is that the rapidly expanding adipose compartment will serve as a reservoir for disposal of excess energy, essentially the reverse of the “overflow hypothesis” described for insulin resistance in obesity (12). Further research needs to be undertaken to elucidate the mechanisms underlying this observation, such as determining the partitioning of nutrients. An appropriate and currently unexplored avenue for this question may be determining the changes in insulin sensitivity in patients with weight regain following bariatric surgery.

Previous studies in lipodystrophic patients and in patients with mutations of the insulin receptor have indicated that leptin therapy is associated with a marked improvement in the metabolic state of the patients with remarkable improvements in insulin sensitivity. This is supported by direct measurement of glucose disposal and suppression of hepatic glucose output before and after leptin therapy as well as the indirect evidence of improved glucose control and/or lowering or discontinuation of insulin therapy. When withdrawal from leptin therapy was attempted in one patient with lipodystrophy, this was accompanied by an immediate worsening of glucose and insulin levels within 48 h of withdrawal (11). However, like those of Paz-Filho et al. (13), these patients are undergoing significant physiological changes with reduction in intrahepatic and intra-
muscular fat, decreased energy intake, and improvement in triglyceride levels (1, 10, 11, 14). Although the overwhelming evidence points toward improved insulin sensitivity in the patients with lipodystrophy, whether these are direct effects of leptin on insulin sensitivity or indirect effects related to other accompanying changes caused by leptin therapy remains to be sorted out in humans.

Given this alternative explanation of findings reported by Paz-Filho et al. (13), along with the positive effect on insulin sensitivity of leptin in patients with lipodystrophy, it is premature to implicate leptin as a contributor to the insulin resistance of obesity. Furthermore, no apparent worsening of glucose metabolism was evident or reported during the trials with recombinant methionyl human leptin (5) and pegylated leptin (6, 7).

Finally, it is certainly understandable why the present studies were not undertaken when subjects were at steady weight. A lengthy withdrawal period to get the subjects to a stable weight is not an ethical approach, taking into consideration all the beneficial effects of leptin therapy in these individuals. Studying insulin sensitivity during a shorter withdrawal period is unlikely to be helpful unless a caloric restriction can be achieved to maintain the reduced weight. These authors should be congratulated for undertaking a difficult set of translational studies in patients with a rare syndrome. Taking the time to design and execute studies in patients who are presented in the community is clearly important. Despite design problems that are inherent in performing research in patients undergoing active treatment for disease, these studies should be supported and published because clearer insights into human diseases will come only from studies in human volunteers.

REFERENCES


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