

EDITORIAL



Another Agent for Obesity — Will This Time Be Different?

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Over the past few decades, obesity has become a global epidemic that affects diverse societies across developed and developing countries. Obesity rates correlate well with recent developments such as incessant enticements to sit and an unprecedented availability, at low or no cost, of foods and beverages rich in poorly satiating calories. These rapid environmental changes interact with preexisting genetic tendencies, yet in a time-scale so brief as to outstrip evolution.

What is wrong with obesity? Extra weight once indicated prosperity and was considered to be attractive. But now we know that overnutrition and underexertion beget a cluster of seemingly unrelated problems labeled “the metabolic syndrome,” which includes, for example, visceral abdominal obesity, dysglycemia, dyslipoproteinemia, and hypertension. Similar amounts of excess weight among people of different races and ethnic groups have varying effects on risk factors, with certain groups hit particularly hard.¹ Although obesity is associated with resistance to the plasma glucose-lowering actions of insulin,² many other metabolic pathways still remain responsive to insulin (i.e., the actions of insulin become imbalanced). Compensatory hyperinsulinemia can drive insulin-responsive effects, such as extracellular signal-regulated kinase (ERK) activation and hepatic de novo lipogenesis, which may cause or worsen features of the metabolic syndrome.³ Moreover, exogenous insulin at high doses has recently attracted interest as a potential cardiovascular risk factor.⁴

Although numerous randomized trials of lifestyle modification, medications, and bariatric surgery have shown that weight loss reduces morbidity,⁵ most patients cannot sustain sufficient weight loss. Despite decades of drug development, the benefits of medications to treat

obesity remain limited because of side effects and inadequate efficacy, especially in the long term. Bariatric surgery results in the most weight loss and the highest rates of remission of type 2 diabetes,⁶ but the potential side effects are of concern. Furthermore, performing bariatric surgery in approximately 400 million obese persons worldwide is not feasible.

Enter another approach: glucagon-like peptide-1 (GLP-1) mimetics stimulate insulin secretion, lower postprandial glucagon levels, slow gastric emptying, and reduce appetite. Many trials have shown that treatment with GLP-1 mimetics also results in clinically significant weight loss.⁷ In this issue of the *Journal*, Pi-Sunyer et al.⁸ report on a large-scale, randomized, double-blind trial of the GLP-1 mimetic liraglutide, administered once daily at a high dose of 3.0 mg, versus placebo for weight management. In December 2014, after reviewing the results of phase 3 trials, including data from the trial by Pi-Sunyer et al., the Food and Drug Administration approved liraglutide as the first GLP-1 mimetic for weight loss in adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher (obese) or a BMI of 27.0 to 29.9 (markedly overweight) and one or more weight-related coexisting illnesses.

Participants in the trial by Pi-Sunyer et al. did not have diabetes and were either obese or markedly overweight with weight-related complications of dyslipoproteinemia, hypertension, or both. More than 60% had prediabetes at enrollment. Liraglutide or placebo was administered in conjunction with lifestyle counseling over the course of 56 weeks to more than 3700 participants from six continents.

At week 56, participants in the liraglutide

group showed significant improvements with respect to all three coprimary end points. Those in the liraglutide group lost a mean of 8.4 kg of body weight, as compared with a loss of 2.8 kg in the placebo group. Moreover, 63% and 33% in the liraglutide group, as compared with 27% and 11% in the placebo group, lost at least 5% and 10%, respectively, of their body weight. The mean differential weight loss of 5.6 kg between the liraglutide group and the placebo group is more than what was observed in previous studies of GLP-1 mimetics, which used lower doses of 1.2 to 1.8 mg per day.⁷ Participants who were randomly assigned to discontinue liraglutide use after 56 weeks of receiving treatment gained, on average, 2.9 kg of body weight in 12 weeks. Longer observation will be needed to see the full extent of this therapeutic reversal.

There were statistically significant, although sometimes quantitatively modest, improvements in secondary end points, which included glycemic control, fasting insulin concentrations, cardiometabolic markers, and quality-of-life measures. Similar benefits were seen in participants with prediabetes and those with normoglycemia and across prespecified BMI categories. In an era of scrutiny for major adverse cardiovascular events with the use of medications, the similar rates of adverse events observed in the liraglutide and placebo groups are reassuring, though the rates were calculated over a short course of follow-up of only 56 weeks. Remarkably, the rate of new diagnoses of diabetes in the liraglutide group was less than one eighth that in the placebo group. A 2-year study extension was performed to pursue this finding, and the data are currently being analyzed.

As expected, the most common side effects were related to the gastrointestinal system and were mild. No increase in calcitonin level and no case of C-cell carcinoma of the thyroid were observed, but longer follow-up is required. The higher number of breast cancers detected in the liraglutide group will also require continued attention. We agree with the plausibility of the authors' hypothesis that greater weight loss might have facilitated the detection of breast cancer.

In summary, this study has shown that 3.0 mg of liraglutide administered once daily in overweight or obese patients who do not have diabetes results in clinically significant weight loss

and improved secondary end points. Given previous disappointments with various weight-loss strategies, these are welcome findings. Still, liraglutide is no cure. Most obese participants stayed obese, reversal of the metabolic syndrome was not quantified, and liraglutide may be required indefinitely, like statins, but with delivery by injection and at a nontrivial cost.

Undoing the detrimental influences of our new environment requires practical strategies for eating less and moving more. Fortunately, even modest loss of body weight of 5 to 10% makes nearly all medical issues more manageable.^{9,10} On the basis of the current study, modest weight loss may now be easier to achieve, yet we await the results from studies with longer follow-up.

Disclosure forms provided by the authors are available with the full text of this article at www.nejm.org.

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