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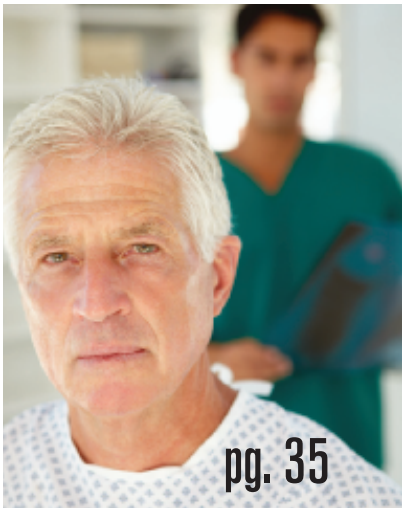

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Bisphosphonates for Osteoporosis: Benefits and Risks

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besity vaccines: A Long Shot?

By Jacqueline Ruttimann, Ph.D., Interim Editor

Got some extra pounds to lose? You're not alone. Currently, one in five adults in the world is overweight—with at least a third of them obese—according to the World Health Organization. If current trends continue, more than half of the U.S. adult population could be obese by 2030.[1]

The reasons for shedding those pounds vary, from losing weight packed on during pregnancy to deflating that spare tire before a college reunion, but the main purpose should be for health. Excess pounds are major risk factors for numerous chronic diseases such as diabetes, cardiovascular disease, and cancer.

Trimming off the fat has historically relied on a trifecta of treatments—diets, pills, and exercise. Yet diets fail, pills carry side effects, and exercise may not be enough. A recent fourth option—bariatric surgery—is prone to complications. A new treatment based on an old method is poised to enter the markets within the next decade or two: obesity vaccines.

"What we are doing at the moment is not satisfactory," said Nikhil Dhurandhar, Ph.D., an associate professor in the Department of Infections and Obesity at the Pennington Biomedical Research Center in Baton Rouge, La. "Current treatment for obesity is like a blanket treatment. If we can find the causes of obesity we could create a direct treatment such as a vaccine."

Why Obesity Vaccines May Stick

Obesity vaccines require a whole new look at the term "vaccine." For most people, vaccines are prophylactic, given early in life to prevent bacterial and viral infections such as diphtheria and measles. This indication harkens back to 2 centuries ago, when Edward Jenner administered fluid from a dairymaid's cowpox skin lesion into his gardener's 8-year-old son and found that the boy was resistant to the smallpox scourge then prevalent (*vaccinia* is Latin for "cowpox").

Vaccines can also be therapeutic, retraining the immune system to attack a condition already present in the body. An example of this vaccine type is Provenge, now on the market for treatment of metastatic, hormone-refractory prostate cancer.

Vaccines could trump the current three weight loss options in that the body's response to vaccines is longer-lasting (on a scale of years rather than weeks or months). Also, the side effects could be similar to those of traditional vaccines: inflammation at the injection site and flu-like symptoms.

Of Mice and Men: Anti-Ghrelin

At first glance, ghrelin does not seem a likely target for an obesity vaccine. Paradoxically, the appetite-stimulating hormone is typically low in obese patients. Yet after diet- or exercise-induced weight loss, its levels surge, contributing to weight regain. Recent research has shown that the long-term success of bariatric surgeries may lie in their ability to suppress this gut hormone.

A research group led by Mariana Monteiro, M.D., Ph.D., at the University of Porto, in Portugal, designed a vaccine against ghrelin by fusing noninfectious, virus-like particles with ghrelin to trigger an immune response—the development of antibodies against ghrelin—that would lower levels of this hormone. Their results were presented in oral and poster presentations at **ENDO 2011: The Endocrine Society's 93rd Annual Meeting** in Boston.

The team vaccinated either normal-weight or diet-induced obese mice three times and compared these animals to control mice that received only saline injections. All the vaccinated mice developed anti-ghrelin antibodies and burned more calories than controls. Within 24 hours of vaccination, the treated mice ate only 82% of the amount eaten by control mice. After the final shot, the vaccinated mice ate only 50% of what the unvaccinated mice consumed. The vaccine also packed a dual punch: Vaccinated mice expressed less neuropeptide Y, another appetite-stimulating hormone. No toxic effects were observed in the mice.

The effects of each vaccination lasted for 2 months, which for a normal 18-month mouse lifespan, corresponds to 4 human years, Dr. Monteiro told ***Endocrine News.***

She expressed caution about whether this vaccine could be a stand-alone treatment for obesity.

"An anti-ghrelin vaccine may become an alternative treatment for obesity, to be used in conjunction with diet and exercise," she said, reiterating that the hormone surge would occur only after the performance of the first two treatment options.

Helping Man and His Best Friend: Somatovac

What if you could melt the fat away without breaking a sweat at the gym? The idea might not be so far-fetched, reported one small biotechnology company about its obesity vaccine.

Designed by Braasch Biotech, the vaccine, Somatovac, creates antibodies that target somatostatin, a hormone that limits the body's production of growth hormone (GH) and insulin growth factor I (IGF-I). A farmload of animals treated with this vaccine, ranging from horses, cows, and pigs, to mice and dogs, show higher levels of GH–releasing hormone and GH. These animals all experienced a build-up of muscle and a breakdown of fat. The growth seen was not completely unregulated; the vaccine attenuates the hormone for 2 weeks, with levels returning to normal afterward. (An added bonus: Cows produced more milk via an increase of their own endogenous hormones, thus possibly replacing the need for recombinant bovine somatotropin, an exogenous hormone that is highly controversial in the dairy industry.)

In collaboration with the Jackson Laboratory, the vaccine or vehicle was administered to a diet-induced obesity mouse model. Six weeks prior and during the study, treated and untreated mice ate similar amounts of mouse chow containing six times the fat content of normal mouse chow. At the study's end, vaccinated mice gained less than half as much weight as controls—equivalent to a vaccinated 200-pound person gaining only between 8 and 14 pounds on a high-fat diet, whereas an unvaccinated person of similar weight gains 30 pounds on the same diet.[2]

"This is akin to someone trying to lose weight but eating a bag of potato chips each day," said Keith Haffer, Ph.D., president and chief scientific officer of Braasch Biotech.

Society Weighs in on Obesity Screening Recommendations

Health care experts are grappling with who should be screened for obesity and when. Late last year, the U.S. Preventive Services Task Force (USPSTF) invited public comments on a draft recommendation stating that clinicians should screen adults for obesity and should offer or refer patients with a body mass index (BMI) greater than 30 kg/m^2 to intensive, multicomponent behavioral interventions. The Endocrine Society submitted comments supporting this recommendation and requesting that the USPSTF expand the recommendation to include patients with a BMI between 25 and 29 kg/m^2 who have risk factors such as glucose intolerance and cardiovascular disease. The Society also recommends that the USPSTF clarify which provider types will be reimbursed for behavioral interventions and to what extent, because these programs are often not covered by insurance until bariatric surgery is deemed necessary. The USPSTF will review all comments before issuing a final recommendation later this year. For more information see *www.uspreventiveservicestaskforce.org/uspstf/uspsobes.htm*.

The effects of each vaccination lasted for 2 months, which for a normal 18-month mouse lifespan, corresponds to 4 human years

Like the anti-ghrelin vaccine, the anti-somatostatin vaccine is envisioned as working in conjunction with lifestyle modification.

Dr. Haffer sees the vaccine being used under close supervision by physicians in obese and morbidly obese individuals with a body mass index over 30.

"After the patients have lost so much weight, they might be motivated to exercise and diet. The vaccine might give them hope that these are viable options," he postulated, adding that if patients are in danger of losing too much weight too quickly while on the vaccine, doctors could reduce its immune stimulatory effect by administering cortical steroids.

Another advantage that this drug has is that it is cheaply made in *Escherichia coli* cells. Dr. Haffer estimates that the dose could cost $10–$20/dose (which would be either monthly or bimonthly)—a major contrast to somatropin (synthetic growth hormone), which totals around $20,000/year for daily injections.

As with all treatments, some should not be treated. The vaccine is counter-indicated in those with a missing GH gene, those who are immunocompromised (e.g., HIV, chronic infection), and those with cancer (IGF-I promotes cancer growth).

Because somatostatin is an archetypal hormone, conserved in all vertebrates from fish to humans, Fido could also be treated with this vaccine. Studies show that obese people often have obese pets, due to lack of exercise and eating the same food as their owners.

Braasch Biotech plans on jointly filing next year to the veterinary and clinical sides of the U.S. Food and Drug Administration.

Infectobesity

Overeating and smoking may have more in common than just being bad habits and contributing to obesity and lung cancer. Both have had to rely on association studies.

"There has never been a single study that shows that smoking causes cancer—just that the weight of evidence is so much that we believe it. The same might be true about infections causing obesity in humans," noted Dr. Dhurandhar, who coined the term "infectobesity" to refer to the fledgling research field that studies the relationship between pathogens and weight gain.

About 10 different microbes have been associated with obesity in various animal models. These include animal and human viruses, bacteria, parasites, and scrapie agents, and the models include insects, chickens, rodents, and non-human primates.[3]

Now, Dr. Dhurandhar and others have identified the first obesity-causing pathogen in humans: adenovirus 36 (Ad36). The first screening study for the presence of Ad36-neutralizing antibodies found a greater prevalence of the virus in obese people (30%) than in non-obese people (11%). When the same groups were screened for other non-adipogenic adenoviral strains, obese people did not have a different amount of the viruses than non-obese people.

In another study involving twins, in whom one was positive for Ad36 and the other negative, the former was heavier than the latter. Two other adenoviruses, Ad37 and Ad5 have also been found to be obesogenic.[3]

Although no vaccine currently exists for Ad36, Ad37, or Ad5, Dr. Dhurandhar theorized that one could be administered in childhood—a time when people get the most adenoviral infections.

He also noted a "ying/yang" when it comes to individuals harboring Ad36. Although these persons are heavier than their Ad36-negative peers, their glycemic control is typically better. Dr. Dhurandhar and his research group have identified the responsible protein—produced by this virus—paving the way for a possible anti-diabetes drug.

Vanquishing Obesity for Good?

We are still decades from being a pinprick away from lowering the rate of worldwide obesity. Even then, the vaccine is not a guaranteed cure-all.

"It's very important to recognize heterogeneity in the field in terms of physiology. One shoe will not fit all—some will have a quick response and some will take longer or have no effect," cautioned Dr. Dhurandhar. ■

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