Who Becomes Obese during Childhood — Clues to Prevention
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The prevalence of childhood obesity in the United States has increased rapidly to historically high levels over recent decades and has begun to plateau in some communities and states. Given such a high prevalence, what are the risk factors that best predict incident obesity in later childhood? What are the contributory characteristics resulting in obesity? Can children at highest risk be targeted accurately for early intervention?

In this issue of the Journal, Cunningham et al. use a unique, nationally representative database to focus on the incidence of obesity and provide a useful perspective on early predictors of obesity from kindergarten through eighth grade. The authors found that early excess weight gain was a key risk factor, since by eighth grade, there was an increased incidence of obesity among children who had entered kindergarten overweight (≥85th percentile of body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] for age and sex), as compared with their normal-weight peers.

Previous longitudinal studies have also shown an increased risk of obesity from excess weight gain as early as the first 6 months of life, and the study by Cunningham et al. adds clear evidence for this risk factor in another longitudinal sample. In addition, the authors examined whether this increased risk among overweight kindergartners varied according to socioeconomic status, race or ethnic group, or birth weight and found no significant differences. The implication for practice is that early excess weight gain is a risk factor for obesity in later childhood across the entire population.

How precise is this risk estimate? The present results indicate that the lower the relative BMI of a given child at kindergarten entrance, the lower the risk of obesity by eighth grade. However, a child who is obese at kindergarten entrance has a 47% risk of being obese by eighth grade, similar to the 54% reported in another national cohort in 2000. When kindergartners at the 99th percentile for weight were followed, 72% were obese by eighth grade. There are technical problems with the determination of a 99th percentile, so it is recommended that clinicians define severe obesity as a BMI of more than 35 or 120% of the age- and sex-specific 95th percentile on the reference standards of the Centers for Disease Control and Prevention. Given the limited evidence for effective treatment of obesity among children under 6 years of age, the limited resources of most clinical settings, and the limited predictive value of the 95th percentile of BMI, severe obesity may be a more useful cutoff for referral to more intensive, multidisciplinary treatment. At the same time, there is the need to continue to improve primary and secondary prevention efforts for children who are overweight (85th to 94th percentile) or more mildly obese (95th percentile to <120% of the 95th percentile).

Clinical interventions are just one approach, since evidence increasingly suggests that multilevel, multisector approaches that focus on children’s environments and that aim to alter early life systems are likely to be most effective in preventing obesity in populations. Such efforts should ideally include cost-effective policy and programmatic interventions across multiple sectors that are feasible and sustainable. Few children are born obese; rather, obesity develops over time, as children progress from infancy to childhood and adolescence. Thus, risk reduction among young children is clearly important, with...
Sclerostin Inhibition for Osteoporosis — A New Approach

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Effective new therapies are still needed for people with osteoporosis. In 2002, the introduction of teriparatide, or recombinant parathyroid hormone (rPTH [1-34]), opened a promising chapter in osteoporosis care.1 For the first time, there was an anabolic agent that significantly increased bone mineral density (BMD), reduced fracture risk, and restored bone architecture back to, or close to, normal. However, despite an impressive track record of both safety and efficacy, teriparatide has had a limited clinical reach as compared with other agents, largely owing to its requirement for daily subcutaneous injection, a black-box warning about osteosarcoma in rats, and its high cost. Since antiresorptive therapies do not restore bone architecture and have a number of other limitations, finding new treatments for osteoporosis has been a high priority.

The results of the study by McClung et al.2 now reported in the Journal represent a potential breakthrough in osteoporosis therapeutics. The study introduces romosozumab, a humanized monoclonal antibody directed against the osteocyte-derived glycoprotein known as sclerostin. Humans with genetic deficiencies of sclerostin and mice with knockout of the sclerostin gene (Sost) have high bone mass, increased bone strength, and resistance to fracture. Sclerostin works by inhibiting the Wnt and bone morphogenetic protein signaling pathways that are critical for osteoblast proliferation and activity. By inhibiting sclerostin, romosozumab should enhance osteoblastic function.

This phase 2 study was a randomized, placebo-controlled trial that included two comparator drugs. Participants were healthy postmenopausal women with osteopenia, randomly assigned to one of eight study groups — romosozumab administered subcutaneously either monthly or every 3 months at various doses; oral alendronate at a dose of 70 mg weekly; subcutaneous teriparatide at a dose of 20 μg daily; or placebo injections given monthly or every 3 months. Primary and secondary end points included changes in BMD as compared with placebo, changes in markers of bone metabolism, and comparisons of the study drug with alendronate and teriparatide.

The results were impressive. As compared with baseline, BMD was significantly improved for all doses of romosozumab and at all sites except at the distal third of the radius, which remained essentially unchanged. At the highest monthly dose of romosozumab, increases in BMD at the spine and hip were rapid and robust, surpassing the BMD values with alendronate and teriparatide at 6 months and remaining significantly higher than the BMD values with either comparator by the end of the trial.

If the changes in BMD for a presumed ana-