Treating obesity seriously: when recommendations for lifestyle change confront biological adaptations

Many clinicians are not adequately aware of the reasons that individuals with obesity struggle to achieve and maintain weight loss,[1] and this poor awareness precludes the provision of effective intervention.[2] Irrespective of starting weight, caloric restriction triggers several biological adaptations designed to prevent starvation.[3] These adaptations might be potent enough to undermine the long-term effectiveness of lifestyle modification in most individuals with obesity, particularly in an environment that promotes energy overconsumption. However, they are not the only biological pressures that must be overcome for successful treatment. Additional biological adaptations occur with the development of obesity and these function to preserve, or even increase, an individual's highest sustained lifetime bodyweight. For example, preadipocyte proliferation occurs, increasing fat storage capacity. In addition, habituation to rewarding neural dopamine signalling develops with the chronic overconsumption of palatable foods, leading to a perceived reward deficit and compensatory increases in consumption.[4] Importantly, these latter adaptations are not typically observed in individuals who are overweight, but occur only after obesity has been maintained for some time.[3] Thus, improved lifestyle choices might be sufficient for lasting reductions in bodyweight prior to sustained obesity. Once obesity is established, however, bodyweight seems to become biologically stamped in and defended. Therefore, the mere recommendation to avoid calorically dense foods might be no more effective for the typical patient seeking weight reduction than would be a recommendation to avoid sharp objects for someone bleeding profusely.

Evidence suggests that these biological adaptations often persist indefinitely, even when a person re-attains a healthy BMI via behaviourally induced weight loss.[3] Further evidence indicates that biological pressure to restore bodyweight to the highest-sustained lifetime level gets stronger as weight loss increases.[5] Thus, we suggest that few individuals ever truly recover from obesity; individuals who formerly had obesity but are able to re-attain a healthy bodyweight via diet and exercise still have 'obesity in remission' and are biologically very different from individuals of the same age, sex, and bodyweight who never had obesity.[3,5] For most individuals, these biological adaptations need to be addressed for weight loss to be sustained long-term. We believe these mechanisms largely explain the poor long-term success rates of lifestyle modification, and obligate clinicians to go beyond mere recommendations to eat less and move more.

Because sustained obesity is in large part a biologically mediated disease, more biologically based interventions are likely to be needed to counter the compensatory adaptations that maintain an individual's highest lifetime bodyweight. For example, leptin replacement therapy can normalise diet-induced reductions in energy expenditure and neural responsivity.[6] However, commercialisation of leptin replacement therapy has not yet been successful. Current biologically based interventions comprise antiobesity drugs, bariatric surgery and, the most recent development, intermittent intra-abdominal vagal nerve blockade. Risk–benefit profiles of antiobesity drugs and bariatric procedures have improved in recent years; however, long-term (>2 year) data for recently approved drugs are still pending. Initial trials suggest that these new drugs might have either lower rates of side effects (lorcaserin) or improved effectiveness (phentermine/topiramate extended-release and bupropion/naltrexone) relative to previous drug treatments;[7,8] however, empirical comparisons have not been made. Liraglutide, an injectable glucagon-like peptide-1 receptor agonist, was also recently approved for long-term weight management. Finally, vagal nerve blockage uses an implanted pacemaker-like device to intermittently block signalling in the gut–brain axis via the abdominal vagus nerve. These interventions do not permanently correct the biological adaptations that undermine efforts for healthy weight loss but do, during use, alter the neural or hormonal signalling associated with appetite to reduce hunger and caloric intake, and can produce a 4–10% weight reduction. Data also suggest that combining antiobesity drugs with more intensive lifestyle modification would probably increase weight loss.[9] The most common surgical options for extreme obesity include Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding. Substantial weight

Raguet H/BSIP/Science Photo Library

Lancet Diabetes Endocrinol 2015

Published Online
February 12, 2015
http://dx.doi.org/10.1016/S2213-8587(15)00009-1