# 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

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*Lancet Diabetes Endocrinol* 2015

Published Online
February 12, 2015
http://dx.doi.org/10.1016/S2213-8587(15)70010-0

***Panel:* authors' clinical recommendations for obesity prevention and treatment***

**Prevention**

- Proactively address prevention with overweight patients. Obesity is far more challenging to address once established and, therefore, clinicians should address the importance of proper nutrition and physical activity prior to the development of obesity.
- Focus on lifestyle choices. Because several biological adaptations that preserve highest lifetime bodyweight do not seem to occur until obesity is sustained, validated behavioural interventions might be sufficient to regulate bodyweight.
- Continue to monitor progress and adjust strategy as necessary. Strategies should be ongoing and take into account the fact that weight-loss maintenance is more difficult than weight loss. Formulate a specific strategy and provide resources for weight-loss maintenance to patients who are overweight and able to achieve weight loss via lifestyle modification.

**Treatment**

- Encourage patients with obesity to consider treatment, even if not the primary complaint. Address the increased risk of serious medical conditions and offer treatment options.
- Consider biologically based interventions. Lifestyle modification alone is likely to be insufficient. Consider medication or surgery when appropriate.
- Implement a multifaceted treatment strategy. Construct an individualised treatment plan involving different treatments which can include highly structured diets, a high-protein diet, increases in physical activity, drugs, and bariatric surgery.
- Recommend surgery when appropriate, because bariatric surgery is the only effective long-term treatment for obesity available. Attempt highly structured lifestyle modification and discuss pharmacotherapy first. Patients for whom lifestyle change is not successful, particularly those with clinically severe obesity, should be informed about the risks and potential benefits of bariatric surgery.
- Continue to monitor progress and adjust treatment strategy as necessary. Formulate a specific strategy and provide resources for weight loss maintenance. Medication can be considered when behavioural weight-loss efforts wane.
- Inform patients of the challenges to weight-loss maintenance. Patients who achieve significant weight loss via lifestyle change are likely to become more metabolically efficient and will have to ingest up to 300 fewer (or burn up to 300 more) calories per day than someone of the same weight who never had obesity, just to maintain that weight. Inform patients that powerful biological mechanisms encourage weight regain and use of biologically based treatments (eg, drugs) is not a reflection of weak will.

*Based in part on recommendations from other sources.[13,14]

loss (roughly 25% initial bodyweight for Roux-en-Y gastric bypass) has been reported up to 20-year follow-up.[10] Further, gastric bypass corrects obesity-induced changes in appetite-related hormone profiles[11] and neural responsivity,[12] which might explain why bariatric surgery is the only available treatment to show long-term effectiveness.

Although helpful, available biologically based interventions are not universally effective in countering the obesity-promoting interaction between a biological predisposition for energy storage and an environment that promotes high energy intake and low energy expenditure. Until substantial changes to the food and activity environment can be made, obesity should be treated as a chronic, and often treatment-resistant, medical disease with biological (and behavioural) underpinnings. Specifically, clinicians should be proactive in addressing obesity prevention with patients who are overweight and, for those who already have sustained obesity, clinicians should implement a multimodal treatment approach that includes biologically based interventions such as pharmacotherapy and surgery when appropriate.[13] The risk–benefit ratio of these biologically based treatments should be established for each patient and weighed against potential risks posed by the patient's comorbid disorders. We recommend the use of lifestyle modification to treat individuals with sustained obesity, but it should be only one component of a multimodal treatment strategy. It is also important for clinicians to note that weight losses of only 5–10% of initial bodyweight are sufficient for clinically meaningful reductions in weight-related biomarkers, despite the fact that this level of weight loss might be disappointing to some patients with more aesthetically-driven goals. Finally, we encourage clinicians to monitor patients' weight-loss progress and adapt treatment strategies over time. Specific plans to maintain lost weight should be developed. For example, an individual might be initially successful in losing weight with lifestyle modification but need pharmacotherapy to sustain clinically meaningful weight loss. See panel for a summary of recommendations for the prevention and treatment of obesity, and the recently published NIH working group report[14] for recommendations for weight loss maintenance. We urge individuals in the medical and scientific community to seek a better understanding of the biological factors that maintain obesity and to approach it as a disease that cannot be reliably prevented or cured with current frontline methods.

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CNO reports grants from Accera, and non-financial support from ProBar. AGT reports non-financial support from Nutrisystem. RFK reports personal fees from Vivus, Takeda, and Novo Nordisk and grants from Weight Watchers. TAW reports personal fees from Nutrisystem, Orexigen Pharmaceutical, Novo Nordisk, Boehringer Ingelheim, Guilford Press, and Shire Pharmaceutical and grants from Novo Nordisk, Weight Watchers, and NutriSystem.

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