

How to reset metabolic setpoint in obesity management

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Abstract

The metabolic setpoint theory is based upon the premise that there is a barohomeostatic mechanism in humans which maintains weight within a predetermined range. This is viewed as an obstacle to weight loss, but can also be considered an opportunity to reset the barometabolic setpoint. This expert clinical opinion piece shares pragmatic suggestions on how to achieve this. Initiating with monotherapy, titrating dosage gradually, interchanging treatment if needed, troubleshooting where necessary and intensifying slowly to combination therapy help reset the barometabolic homeostatic range.

Keywords: Barocrinology, GLP1RA, Intensive behavioural therapy, Liraglutide, Overweight, Obesity, Semaglutide.

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Introduction

Obesity has reached pandemic proportions involving developed and developing countries alike.¹ While newer weight loss therapies continue to emerge, long term maintenance of weight loss is the biggest challenge in the management of obesity.² The metabolic setpoint theory suggest that there is a barohomeostatic mechanism in humans which is ensured by regulation of appetite and energy expenditure. When there is a change in body weight this set point drives the energy expenditure and appetite towards the opposite direction.³ The existence of a metabolic setpoint explains why many people find it difficult to reduce weight. It also helps us understand why 'desired' weight, optimal weight, and 'realistic' weight are different. The metabolic setpoint is not necessarily set at a specific weight: it may be a range of weight, varying a few kilograms around a central point. The metabolic setpoint theory is as relevant for weight loss as it is for weight gain. The drivers for regain of lost weight, unfortunately, seems to be stronger than those for loss of gained weight and this may gradually change the set point at a higher weight, over time.

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The metabolic setpoint theory is supported by both animal and human studies. Observational and randomised controlled trials have shown that people who reduce weight tend to regain it as soon as intensive &/or short-term interventions are over.⁴ Multiple mechanisms have been proposed to explain the metabolic setpoint, such as leptin secretion and sensitivity, changes in energy expenditure, regulation of orexigenic hormones.⁵ Though metabolic setpoint has been primarily studied for obesity, it has been also described for other metabolic disorders.⁶⁻⁹

Obstacle or opportunity?

The metabolic setpoint can be viewed as an obstacle, or as an opportunity, for obesity care. The hindrance is easy to understand: efforts at weight loss have to overcome internal barohomeostatic mechanisms. The dual intervention theory tries to explain how the setpoint, or rather, the set range, can be utilized to promote weight optimization. The dual intervention theory proposes the existence of two levels: a higher weight boundary, and a lower weight boundary, which are determined by different factors. The classic dual intervention theory suggests that the higher limit is decided by the risk of succumbing to predators, if overweight reduces the ability to run. The lower limit is a response to the threat of extinction due to starvation.¹⁰

In the modern world, different forces come into play. The upper weight boundary is an expression of hedonistic forces (availability and accessibility of high calorie food), while the minimum maintainable weight is related to homeostatic force (appetite and energy expenditure regulation). A gradual barometabolic drift (rather than a sudden shift) may succeed in resetting the higher cut-off or set point of weight. Glucagon-like peptide 1 receptor agonists (GLP1RA) act upon the hypothalamus by activating central anorexigenic pathways including the pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) receptors in the arcuate nucleus. These pathways have been targeted to alter the metabolic setpoint.¹¹

Pragmatic suggestions

An understanding of the complex mechanisms which balance and counter-balance weight loss and gain, allows us to suggest the following strategies to reset the

Table: Tactics to reset the metabolic setpoint.

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- Talk about realistic goals and targets of obesity care
 - Assess etiology, risk factors and complications of obesity
 - Craft appropriate management strategy, choosing best-in-class monotherapy medication
 - Titrate dose slowly and steadily
 - Interchange treatment if safety and tolerability are compromised
 - Combination therapy if expected results are not achieved
 - Smart trouble shooting as and when required
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metabolic setpoint (Table).

• Initiation

- ♦ Begin with one intervention, e.g, medical nutrition therapy (MNT) and/or exercise
- ♦ Increase the intensity of calorie deprivation and/or exercise at gradual intervals
- ♦ Once a plateau is achieved, add a new modality of treatment, e.g, medical grade MNT or pharmacotherapy
- ♦ Offer variety in diet and physical activity
- ♦ Initiate mono-pharmacotherapy at the lowest dose possible, and escalate the dose at regular intervals, till maximally tolerated or maximal dose is attained. Choose best-in-class medication

• Maintenance

- ♦ Continue with intensive behavioural therapy and lifestyle modification measures
- ♦ Assess obstacles to weight loss, and address them appropriately
- ♦ Interchange/shift to other pharmacotherapeutic agent if expected efficacy, safety or tolerability is not achieved
- ♦ Long term follow up as for any other chronic disease like diabetes, hypertension or osteoporosis.
- ♦ To ensure comorbidities are treated with weight friendly drugs

• Intensification

- ♦ Reinforce need for behavioural modification and adaptation
- ♦ Consider interchange to a better drug from the same class
- ♦ Intensify by adding another drug, from a different class

- ♦ Optimise the dose of all drugs as per safety and tolerability
- ♦ Revisit goals and targets of obesity management.

Summary

The metabolic setpoint concept which can be used to create realistic targets, techniques and tactics for obesity care. Understanding this theory of barohomeostasis allows the person living with obesity, and the obesity care provider, to work together to achieve realistic health goals, in an optimized manner.

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