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Obesity (Silver Spring). Author manuscript; available in PMC 2025 June 01.

Published in final edited form as:

Obesity (Silver Spring). 2024 June ; 32(6): 1163–1168. doi:10.1002/oby.24027.

Physiology of the Weight Loss Plateau in response to Diet Restriction, GLP-1R Agonism, and Bariatric Surgery

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Abstract

Objective: To investigate why different weight loss interventions result in varying durations of weight loss prior to approaching plateaus.

Methods: A validated mathematical model of energy metabolism and body composition dynamics was used to simulate mean weight and fat loss trajectories in response to diet restriction, semaglutide 2.4 mg, tirzepatide 10 mg, and Roux en-Y gastric bypass (RYGB) surgery interventions. Each intervention was simulated by adjusting two model parameters affecting energy intake to fit the mean weight loss data. One parameter represented the persistent shift of the system from baseline equilibrium and the other parameter represented the strength of the feedback control circuit relating weight loss to increased appetite.

Results: RYGB surgery resulted in a persistent intervention magnitude more than 3-fold greater than diet restriction and about double that of tirzepatide and semaglutide. All interventions except diet restriction substantially weakened the appetite feedback control circuit resulting in an extended period of weight loss prior to the plateau.

Conclusions: These preliminary mathematical modeling results suggest that both GLP-1 receptor agonism and RYGB surgery interventions act to weaken the appetite feedback control circuit regulating body weight and induce greater persistent effects to shift the body weight equilibrium as compared to diet restriction.

Introduction

Every obesity intervention eventually results in a body weight plateau after which no further weight loss occurs. The timing of the plateau is a subject of great interest, especially in the context of the recently introduced GLP-1 receptor agonists that exhibit ongoing weight loss without an obvious plateau until well after 12 months (1, 2). Similarly, bariatric surgery often results in a prolonged period of weight loss, whereas diet interventions typically exhibit plateaus within ~12 months. What explains these differing weight trajectories?

Here, I used a validated mathematical model of energy balance and body composition dynamics (3) to simulate the mean weight loss kinetics in response to a variety of

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DISCLOSURE: The author declares no conflict of interest

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interventions within the context of a physiological system that regulates body weight via feedback control of both energy intake and expenditure (4, 5). Specifically, I sought to quantify the magnitude of interventions involving diet restriction, semaglutide, tirzepatide, and Roux en-Y gastric bypass (RYGB) surgery by simulating mean responses in published studies. Preliminary results suggest that, unlike diet restriction, semaglutide, tirzepatide, and RYGB weaken the appetite feedback control circuit by ~40–70% thereby resulting in an extended period of weight loss prior to the plateau.

Methods

A previously published and validated mathematical model of human energy metabolism and body composition dynamics (3, 6) was recently modified to represent feedback control of energy intake in response to interventions that induce negative energy balance (4, 5). Since most weight loss interventions in humans mainly affect energy intake, I modeled the interventions as follows:

$$\Delta I(t) = -P(t) - k \times \Delta W(t)$$

where ΔI(t) is the change in energy intake over time relative to the weight maintenance baseline, P(t) is a parameter that shifts the system away from the baseline equilibrium, and k is a feedback gain parameter relating appetite to weight change, ΔW(t). In the absence of an intervention, P(t) = 0 and k = 95 kcal/d per kg corresponding to the baseline strength of the feedback circuit controlling appetite as previously estimated from modeling weight loss trajectories during sodium glucose co-transporter 2 (SGLT2) inhibition (5). Note that this modeling approach does not specify the mechanisms by which interventions result in changes in energy intake but rather seeks to quantify the effects of the interventions within the context of a physiological system with dynamic adaptations of energy expenditure and proportional feedback control of appetite.

Mathematical model simulations were initialized using mean baseline anthropometric data from published studies on intensive calorie restriction (7), dietary macronutrient restriction (8), RYGB surgery (9), semaglutide (2), and tirzepatide (1) assuming a mean baseline free-living physical activity level of 1.65 (10). Each intervention was simulated by fitting the parameters P(t) and k such that the modeled body weight time courses matched the observed mean weight trajectories. Body fat was measured by dual energy X-ray absorptiometry in all published intervention studies and mean body fat loss data was compared to model simulations that assumed nonlinear partitioning between lean and fat tissues originally described by Forbes (11).

To simulate RYGB surgery and intensive calorie restriction, P(t) was assumed to be single parameter value for time t>0. Given the similar weight loss trajectories for the low carbohydrate and low fat diet restriction groups, I combined the diet restriction groups from the DIETFITS trial and used a constant effect for $P(t) = P_0$ for the first 3 months followed by a gradual reduction of diet adherence to match the mean self-reported intake changes (8). Specifically, I assumed a linear reduction from month 3 to $0.86 \times P_0$ at 6 months followed by a linear reduction to $0.78 \times P_0$ at 12 months. To simulate escalating doses of semaglutide and

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tirzepatide, $P(t) = P_0 + (P_{max}-P_0)t/T$ until t=T, where P_0 is the initial drug effect and time t=T is the end of the dose escalation period, after which $P(t) = P_{max}$ indicating the maximum drug effect. Predicted changes in energy intake and total energy expenditure were compared with mean data at corresponding time points, where available.

A linearized version of the mathematical model used in the present study has been previously described (3) and the characteristic exponential time scale of the linear system is $\tau = \rho/(k+\varepsilon)$, where ρ is the effective energy density of the weight change, and ε defines the change in energy expenditure per unit weight change and includes the metabolic adaptation to weight loss. Values for ρ and ε were determined from the baseline anthropometrics and physical activity as previously described (3). The long term change in body weight in the linearized model is given by $-P(\infty)/(k+\varepsilon)$, where $P(\infty)$ is the long term value of the parameter defining the magnitude of the intervention to shift the system from the baseline equilibrium.

Results

To simulate the intensive calorie restriction intervention in the CALERIE phase 2 study (7), the best fit model parameters were k = 82 kcal/d per kg and P(t) = 830 kcal/d resulting in a body weight change trajectory that plateaued after about 12 months with simulated body fat being slightly greater than the mean observed values (Figure 1A). Figure 1B shows a substantial initial decline of energy intake at the onset of the intervention followed by an increase over time that closely matched observed mean energy intake changes obtained using the intake balance method (12). Simulated total energy expenditure rapidly decreased after the intervention onset and thereafter maintained an approximately constant level over the remainder of the 24-month intervention and matched the mean energy expenditure data reasonably well.

Diet restriction in the DIETFITS study (8) was simulated by the best fit parameters k = 101 kcal/d per kg and P_0 = 1200 kcal/d after accounting for waning diet adherence assessed by self-reported intake changes. This resulted in a body weight change plateau within 12 months with slightly more simulated body fat loss than was observed (Figure 1C). Figure 1D illustrates the simulated changes in energy intake and expenditure.

Tirzepatide therapy was simulated using best fit parameters k = 48 kcal/d per kg, P_0 = 830 kcal/d, and P_{max} = 1560 kcal/d after the 12-week dose escalation period (1) resulting in an expected mean weight change plateau after about 24 months (Figure 1E). Tirzepatide therapy resulted in changes in mean values for body fat that were only slightly higher than the simulated values. Tirzepatide simulations resulted in a rapid initial decrease in energy intake that and further declined during the dose escalation period after which intake increased until approaching the simulated energy expenditure towards the end of the 24-month simulation (Figure 1F).

Simulation of semaglutide therapy (2) was achieved using best fit parameters k = 49 kcal/d per kg, P_0 = 610 kcal/d, and P_{max} = 1300 kcal/d after the 16-week dose escalation period resulting in an expected weight change plateau about 24 months after the intervention

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onset (Figure 1G). Energy intake decreased at the onset of the intervention and further declined during the dose escalation period after which intake increased until approaching the simulated energy expenditure towards the end of the 24-month simulation (Figure 1H). Unlike the simulations of the other weight loss interventions, the model predicted substantially lower levels of body fat than the mean values observed following the semaglutide intervention. This indicated a possible semaglutide-induced alteration in energy partitioning. To account for this effect, I fit both the observed mean body weight and body fat changes during semaglutide therapy (not shown) which required adjusting the energy partitioning parameter by ~3-fold from its baseline value originally described by Forbes (11). The revised best fit model parameters after making this adjustment in energy partitioning were k = 31 kcal/d per kg, P_0 = 535 kcal/d, and P_{max} = 1040 kcal/d after the 16-week dose escalation period.

RYGB surgery was simulated using best fit parameters k = 58 kcal/d per kg and P = 3600 kcal/d which resulted in the greatest weight loss and a plateau at 24 months with measured mean body fat changes were only slightly greater than the simulated values (Figure 1I) (9). Energy intake decreased by a very large amount after the surgery corresponding to almost no food intake immediately after the surgery followed by an increase over time to approach total energy expenditure after about 24 months. Modelled total energy expenditure decreased by ~150 kcal/d more than was measured using a respiratory chamber (Figure 1J).

Table 1 summarizes the best-fit model parameters P and k used to match the observed mean body weight trajectories as well as the estimated long term body weight change calculated using the linearized model parameters ρ, ε, and τ assuming that physical activity was maintained and the parameter P continued indefinitely.

Discussion

Weight loss interventions need to be considered within the context of the dynamic physiological system controlling both energy intake and expenditure. Each intervention simulated by the mathematical model assumed persistent effects to decrease energy intake from baseline, but energy intake subsequently increased to eventually match energy expenditure resulting in a weight plateau. The magnitude of the persistent intervention that shifts the system from its baseline equilibrium was more than 3-fold greater following RYGB surgery as compared with diet restriction and about double that of tirzepatide which was slightly larger than semaglutide. While intensive calorie restriction achieved the smallest intervention magnitude, the study participants exerted a substantial persistent effort to cut ~800 kcal/d from their baseline diet. The approximately exponential rise in energy intake after the start of the intervention shows that the same amount of effort to cut calories was met with increasing resistance as ongoing weight loss increasingly activated the feedback control circuit stimulating appetite. Within 12 months this resistance, together with decreased total energy expenditure, matched the persistent effort to cut calories and weight loss plateaued. In the macronutrient diet restriction study, gradual loss of diet adherence was superimposed on the feedback control circuit thereby resulting in an earlier body weight plateau. Thus, the timing of the weight loss plateau is determined by both the strength of

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the feedback circuit controlling appetite together with the (perhaps waning) effect of the intervention magnitude to shift the system from its baseline equilibrium.

Why did the other interventions result in prolonged weight loss periods with plateaus well after 12 months? Interestingly, the mathematical model suggests that the time to reach a weight plateau has nothing to do with the magnitude of the intervention, P, after it reaches a constant value. Rather, a linearized version of the mathematical model used in the present study shows that the characteristic time scale of the system is given by $\tau = \rho/(k + \varepsilon)$, where ρ is the effective energy density of the weight change, ε defines the change in energy expenditure per unit weight change (including metabolic adaptation to weight loss), and k is the appetite feedback gain parameter (4). If k decreases because of the drug and surgery interventions, representing a weakening of the appetite feedback control circuit, then τ increases indicating an extension of the time to reach the weight plateau. Furthermore, the linearized model estimates that the amount of weight lost at the plateau is given by $-P(\infty)/(k + \varepsilon)$, indicating that a decrease in the appetite feedback control parameter k acts along with the parameter defining the long-term magnitude of the intervention to shift the system from the baseline equilibrium, P(∞), to decrease body weight.

The preliminary estimate of k = 95 kcal/d per kg weight loss derived using data from SGLT2 inhibition (5) was reasonably close to the best fit value of k = 83 kcal/d per kg weight loss achieved by calorie restriction in the CALERIE phase 2 trial as well as the k = 101 kcal/d per kg weight loss in the DIETFITS macronutrient restriction trial and resulted in the weight plateaus within 12 months. However, RYGB surgery, semaglutide, and tirzepatide all resulted in much lower values of k of ~30–60 kcal/d per kg suggesting that these interventions weakened the feedback control of appetite by ~40–70% and thereby resulted in a prolonged period of weight loss prior to the plateau.

Another way to increase the characteristic time τ to approach a weight plateau or the magnitude of weight lost at the plateau would be to decrease the value of the parameter ε defining how energy expenditure changes per unit weight loss. However, there is a limited ability to decrease ε because the values were less than ~25 kcal/d per kg. Because the model simulations reasonably matched the mean energy expenditure data, there was no indication that ε was changed from its baseline value and the observed prolongation of the time to approach a reduced weight plateau with RYGB surgery, tirzepatide, and semaglutide is most likely due to a weakening of the feedback control of appetite rather than an alteration of energy expenditure.

The mathematical model of energy partitioning depends on body fat and the magnitude of weight change as previously described (3). The simulated body fat changes generally matched the data quite well except for the semaglutide intervention where mean loss of body fat was substantially less than predicted by the model. Thus, a greater than expected proportion of fat-free mass was lost with semaglutide treatment and more research is needed to investigate body composition changes during semaglutide treatment and whether the composition of fat-free mass lost has functional implications.

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Simulated free-living energy intake and expenditure changes with calorie restriction matched the observations reasonably well, but mean changes in energy expenditure following RYGB surgery measured using respiratory chambers was slightly less than predicted by the model. This may be indicative of an effect of bariatric surgery to preserve energy expenditure or perhaps the respiratory chamber data did not fully capture the changes in energy expenditure in free-living people. Unfortunately, model simulations of energy intake and expenditure for tirzepatide and semaglutide treatment could not be compared with data because such measurements are not yet available.

This study has several limitations. First, its focus was on group average responses, ignoring substantial individual variability characteristic of all weight loss interventions. Previous attempts to mathematically model energy balance dynamics in individuals during diet restriction revealed that the imprecision of energy expenditure and body composition measurements results in insufficient model constraints at the individual level (6). Thus, mechanistic determinants of individual long-term weight loss and body composition variability are presently unclear and beyond the scope of the current study. Another limitation regards the lack of specificity regarding the modeled feedback control of appetite that does not presently account for its molecular mechanisms or whether these appetite signals are associated with loss of body fat, fat-free mass, or something else. Furthermore, I have assumed a linear feedback control of appetite as weight is perturbed away from its baseline equilibrium which may be overly simplistic.

In conclusion, varying model parameters P and k that affect energy intake alone were sufficient to simulate body weight trajectories during a variety of weight loss interventions. The simulations indicated that RYGB surgery, tirzepatide, and semaglutide interventions substantially weakened the feedback control of appetite unlike diet restriction interventions. The persistent magnitudes of these interventions to shift the system from its baseline equilibrium were quantified and varied by more than 3-fold, but even the intensive calorie restriction intervention corresponded to a persistent effect to cut energy intake by ~800 kcal/d over the two-year simulations. Our previous modeling analyses of obesity pharmacotherapies illustrated that after an early reduction in energy intake an approximately exponential increase over time is the expected result of a constant magnitude intervention superimposed on a physiological system with proportional feedback control of appetite (4, 13). However, our previous analyses did not address the question of the timing of the weight loss plateau or its implications regarding the effect of the intervention on the feedback control circuit. Interestingly, the model simulations do not predict any weight regain when assuming fixed values of the model parameters during the latter stages of the interventions. This suggests that explaining weight regain requires additional assumptions about waning adherence to the interventions, tachyphylaxis, or changes in physiology or the environment beyond the scope of the present study.

FUNDING:

This work was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Diabetes & Digestive & Kidney Diseases.

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What is already known about this subject?

- All weight loss interventions eventually result in a weight plateau with no further weight loss despite continued intervention.
- The timing of the weight plateau varies between interventions, with some interventions requiring substantially more than 1 year to approach the plateau.

What are the new findings in your manuscript?

- Mathematical modeling was used to simulate body weight trajectories, body composition and energy balance dynamics of diet restriction, GLP-1 receptor agonism, and bariatric surgery interventions.
- The timing of the weight plateau was mainly determined by the intervention's ability to alter the strength of the feedback control circuit relating weight loss to increased appetite.

How might your results change the direction of research or the focus of clinical practice?

- These results emphasize that weight loss interventions need to be considered within the context of a dynamic physiological system controlling both energy intake and expenditure.
- Basic research and clinical practice may be influenced by attaining a greater appreciation for the physiological resistance to weight loss interventions and how they play out over time.

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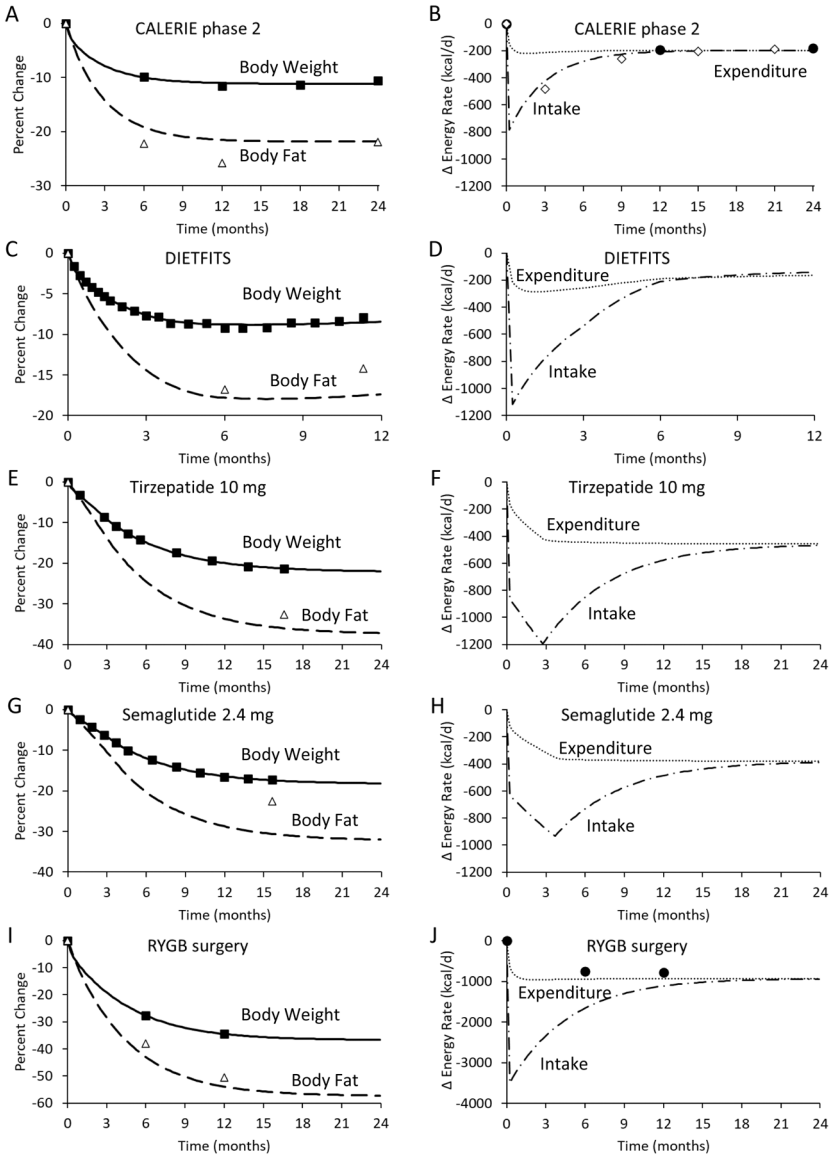


Figure 1.

Body composition and energy balance dynamics during intensive calorie restriction (A and B), macronutrient restriction (C and D), tirzepatide 10 mg (E and F), semaglutide 2.4 mg (G and H), and RYGB surgery (I and J). Simulated body weight is depicted in the solid curves and was fit to the mean data depicted as closed boxes. The dashed curves are the simulated body fat changes and the mean body fat changes measured by DXA are indicated by open triangles. Dotted curves indicate simulated energy expenditure changes and mean data are depicted by solid circles, where available. Dashed dotted curves represent the simulated energy intake changes and the open diamonds depict the mean energy intake data, where available.

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Table 1.

Model parameters that simulate mean weight loss trajectories.

	Calorie restriction	Diet restriction	Tirzepatide 10 mg	Semaglutide 2.5 mg (baseline energy partitioning)	Semaglutide 2.5 mg (adjusted energy partitioning)	RYGB surgery
Parameters adjusted to fit to the observed mean body weight trajectories						
P_0	830	1200	830	610	535	3600
P_{max} (kcal/d)	830	1200	1560	1300	1040	3600
k (kcal/d per kg)	82	101	48	49	31	58
Linearized model parameters determined by baseline anthropometrics and physical activity						
ρ (kcal/g)	9.6	10.3	10.9	10.8	8.8 *	11.3
ε (kcal/d per kg)	24	21	19	19	24 *	19
τ (days)	91	85	162	160	161	147
Long term weight change (kg)	−7.8	−7.7	−23.2	−19.1	−19.1	−47.2

* Adjusting the energy partitioning parameter affected the linearized model parameters ρ and ε.