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Supplementary webappendix

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Dynamic Mathematical Model of Body Weight Change in Adults

Early Phase of Weight Change

To accurately simulate the early changes of body weight that often occur within the first few weeks of a reduced energy diet,¹ we developed a simple model of how diet changes effect body glycogen and body fluids. A more comprehensive computational model accounting for body water changes and the influence of various metabolic fluxes on glycogen content was previously developed by our research group^{2,3} and here we present a simplified model of these effects.

Glycogen is the body's storage form of carbohydrate every gram of glycogen is stored with ~2.7 grams of water.⁴ At baseline, the body contains ~500 g of glycogen and its dynamics are a complex function of various metabolic fluxes such as gluconeogenesis and carbohydrate oxidation. However, a primary determinant of the glycogen content is the dietary carbohydrate intake rate and we propose the following simple approximate model for glycogen dynamics:

$$\rho_G \frac{dG}{dt} = CI - k_G G^2 \quad (1)$$

The parameter $\rho_G = 17.6$ MJ/kg is the energy density of glycogen, G , and the parameter $k_G = CI_b/G_{init}^2$ ensures that dietary carbohydrate intake, CI , at its baseline value, CI_b , gives rise to a stable initial glycogen, G_{init} . The quadratic glycogen term was chosen such that an approximately three-fold increase of CI is required to increase glycogen by a factor of ~1.8 based on carbohydrate overfeeding studies with indirect calorimetry to calculate carbohydrate balance.^{5, 6} To model the effect of glycogen changes on intracellular fluid volume and body weight, we accounted for the ~2.7 grams of water stored with each gram of glycogen.⁴

Extracellular fluid, ECF , can change as a consequence of maintaining sodium homeostasis and the following equation models this effect:

$$\frac{dECF}{dt} = \frac{1}{[Na]} (\Delta Na_{diet} - \xi_{Na} (ECF - ECF_{init}) - \xi_{CI} (1 - CI/CI_b)) \quad (2)$$

where $[Na] = 3.22$ mg/ml is the extracellular sodium concentration, ΔNa_{diet} is the change of dietary sodium in mg/d, $\xi_{Na} = 3000$ mg/L/d and $\xi_{CI} = 4000$ mg/d describes the effect of changes of dietary carbohydrate intake on renal sodium excretion.³

Energy Partitioning between Body Fat and Lean Tissue

Changes of body fat (F) and lean (L) tissue masses are described by the following pair of differential equations:

$$\begin{aligned}\rho_F \frac{dF}{dt} &= (1-p) \left(EI - EE - \rho_G \frac{dG}{dt} \right) \\ \rho_L \frac{dL}{dt} &= p \left(EI - EE - \rho_G \frac{dG}{dt} \right)\end{aligned}\tag{3}$$

The energy partitioning equation 3 accounts for the energy stored in glycogen as described by equation 1. The energy intake rate is EI and the total energy expenditure rate, EE , is described below. The energy content per unit change of body fat or lean tissue mass is $\rho_F = 39.5$ MJ/kg and $\rho_L = 7.6$ MJ/kg, respectively.⁷ The dimensionless energy partitioning function is given by $p = C/(C+F)$ with $C = 10.4 \text{ kg} \times \rho_L/\rho_F$ in accordance with a nonlinear model of body composition change.⁸⁻¹⁰ If the initial body fat mass is unknown, the model uses the measured height, H , and BW to estimate the initial F using the regression equations of Jackson et al. for men and women, respectively:¹¹

$$\begin{aligned}F_m &= \frac{BW}{100} \left[0.14 \times age + 37.31 \times \ln(BW/H^2) - 103.94 \right] \\ F_w &= \frac{BW}{100} \left[0.14 \times age + 39.96 \times \ln(BW/H^2) - 102.01 \right]\end{aligned}\tag{4}$$

Where BW is in kg, H is in meters, and age is in years. The initial lean body mass is simply the difference between the initial BW , the initial F , the initial ECF , and the initial G and its associated water.

The total energy expenditure rate, EE , is given by:

$$EE = K + \gamma_F F + \gamma_L L + \delta BW + TEF + AT + \eta_L \frac{dL}{dt} + \eta_F \frac{dF}{dt}\tag{5}$$

where K is a constant determined by the initial energy balance condition, $\gamma_F = 13$ kJ/kg/day and $\gamma_L = 92$ kJ/kg/day are the regression coefficients relating resting metabolic rate versus body fat and lean mass, respectively.¹² The parameters $\eta_F = 750$ kJ/kg and $\eta_L = 960$ kJ/kg account for the biochemical efficiencies associated with fat and protein synthesis¹³ assuming that the change of lean body mass is primarily accounted for by body protein and its associated intracellular water.⁷

Diet changes resulted in immediate changes in the thermic effect of feeding, TEF:

$$TEF = \beta_{TEF} \Delta EI \quad (6)$$

$\beta_{TEF} = 0.1$ represents the typical assumption of ~10% TEF.¹⁴ Adaptive thermogenesis, AT , included changes of energy expenditure with energy intake changes, ΔEI , over and above those expected from body composition changes alone.^{2, 3} We modeled this as follows:

$$\tau_{AT} \frac{dAT}{dt} = \beta_{AT} \Delta EI - AT \quad (7)$$

where $\beta_{AT} = 0.14$ was determined in our previous steady state analysis of longitudinal weight loss studies¹⁵ and $\tau_{AT} = 14$ days sets the timescale for adaptive thermogenesis dynamics.^{2, 3}

The parameter δ represents physical activity and a value of ~30 kJ/kg/d corresponds to an average sedentary person. Note that the energy cost of physical activity for most activities is assumed to be proportional to the body weight.¹⁴ We estimated the parameter δ by assuming a sedentary physical activity level (PAL) of 1.5 which is defined as the ratio of the total energy expenditure rate, EE , divided by the resting metabolic rate (RMR) which was estimated using the Mifflin-St. Jeor regression equations.¹⁶ The parameter δ was then calculated as:

$$\delta = [(1 - \beta_{TEF}) \times PAL - 1] RMR / BW \quad (8)$$

where we have accounted for the baseline TEF .

Since EE is a function of the rates of change of L and F which themselves depend on EE , we substitute equations 3 into equation 5 and solve for EE closed form expression for EE :

$$EE = \frac{K + \gamma_F F + \gamma_L L + \delta BW + TEF + AT + (EI - \rho_G dG/dt) [p\eta_L / \rho_L + (1-p)\eta_F / \rho_F]}{1 + p\eta_L / \rho_L + (1-p)\eta_F / \rho_F} \quad (9)$$

Model Validation and Web-based Implementation

As described in the main text, the model was validated by comparing model predictions with the results from human feeding studies that were not used for model development.¹⁷⁻

¹⁹ The model was implemented using Java in a web-based simulation tool that can be used to predict the effects of interventions on body weight change over time and can be accessed at the following URL: <http://bwsimulator.niddk.nih.gov>

Characteristic Time Constant for Long Term Body Weight Change

Glycogen levels and *ECF* stabilize, and the adaptive thermogenesis term, *AT*, approaches steady state after the first several weeks following a step change of diet. Therefore, the glycogen flux terms in equations 3 and 9 become negligible and the *AT* approaches $\beta_{AT}\Delta EI$.

Therefore, the second phase of weight change can be captured by the linearized version of the above model:²⁰

$$\left[\frac{\eta_F + \rho_F + \alpha\eta_L + \alpha\rho_L}{(1-\beta)(1+\alpha)} \right] \frac{dBW}{dt} = \Delta EI - \frac{1}{(1-\beta)} \left[\frac{\gamma_F + \alpha\gamma_L}{(1+\alpha)} + \delta \right] (BW - BW_0) \quad (10)$$

The parameter $\beta = \beta_{AT} + \beta_{TEF}$ and the parameter α represents the relationship between changes of lean and fat mass:⁸ $\alpha \equiv dL/dF = C/F$ where $C = 10.4$ kg is the Forbes parameter. For modest weight changes, α can be considered to be approximately constant with F fixed at its initial value F_0 .¹⁰ The larger the initial fat mass, F_0 , the smaller the parameter α . The linearized model can therefore be written as:

$$\rho \frac{dBW}{dt} = \Delta EI - \varepsilon (BW - BW_0) \quad (11)$$

where ρ is an effective energy density associated with the BW change and ε is a parameter that defines how energy expenditure depends on BW :

$$\rho = \frac{\eta_F + \rho_F + \alpha\eta_L + \alpha\rho_L}{(1-\beta)(1+\alpha)} \quad (12)$$

and

$$\varepsilon = \frac{1}{(1-\beta)} \left[\frac{\gamma_F + \alpha\gamma_L}{(1+\alpha)} + \delta \right] \quad (13)$$

Therefore, the linearized equation can be written as:

$$\frac{dBW}{dt} = \Delta EI / \rho - (BW - BW_0) / \tau \quad (14)$$

where the time constant, $\tau \equiv \rho / \varepsilon$, defines the characteristic time scale of weight change. Therefore, the time constant is given by:

$$\tau = \frac{\eta_F + \rho_F + \alpha(\eta_L + \rho_L)}{\gamma_F + \delta + \alpha(\gamma_L + \delta)} \quad (15)$$

Note that the physical activity parameter, δ , appears only in the denominator and the time constant clearly decreases for increasing physical activity. Therefore, increased physical activity speeds up the approach to steady-state body weight.

The dependence of the time constant on the initial body composition is through the parameter $\alpha \equiv dL/dF \approx C/F_0$:

$$\frac{\partial \tau}{\partial \alpha} = \frac{(\eta_L + \rho_L)(\gamma_F + \delta)}{[\gamma_F + \delta + \alpha(\gamma_L + \delta)]^2} - \frac{(\eta_F + \rho_F)(\gamma_L + \delta)}{[\gamma_F + \delta + \alpha(\gamma_L + \delta)]^2} \quad (16)$$

Since all the parameters are positive and magnitude of the second term is always larger than the first term for realistic model parameters, the partial derivative of τ with respect to α is negative implying that the time constant increases for increasing body fat.

Diet versus Physical Activity for Weight Loss

At steady state, $dF/dt = dL/dt = 0$ and $\Delta EE = \Delta EI$. Therefore, equation 11 can be solved for the eventual change of body weight, ΔBW :

$$\Delta BW = \frac{(1 - \beta) \Delta EI - BW_{init} \Delta \delta}{\delta_{init} + \Delta \delta + \gamma_L - \Phi(\gamma_L - \gamma_F)} \quad (17)$$

where $\Delta \delta$ is the change of physical activity and $\Phi \equiv \Delta F / \Delta BW$ defines the composition of the steady state BW change as previously described.¹⁰ Because Φ increases with increasing initial body fat, F_0 , and $\gamma_L > \gamma_F$, greater weight changes result for larger F_0 because the denominator of equation 17 gets smaller.

Now consider the relative impact of a step decrease of energy intake, $\Delta EI = -\Gamma$, with an initially energy equivalent step increase of physical activity, $\Delta \delta = \Gamma / BW_{init}$, where Γ is a constant defining the magnitude of the intervention. Equation 17 defines an intervention magnitude leading to equivalent weight loss via increased physical activity or decreased dietary intake:

$$\Gamma = \frac{\beta}{1 - \beta} [\delta_{init} + \Phi \gamma_F + (1 - \Phi) \gamma_L] BW_{init} \quad (18)$$

When Γ is below this value then physical activity leads to greater weight loss than diet and when Γ exceeds this value then diet restriction leads to greater weight loss than physical activity.

References

1. Heymsfield SB, Thomas D, Nguyen AM, Peng JZ, Martin C, Shen W, et al. Voluntary weight loss: systematic review of early phase body composition changes. *Obes Rev.* 2010.
2. Hall KD. Computational model of in vivo human energy metabolism during semistarvation and refeeding. *Am J Physiol Endocrinol Metab.* 2006; **291**(1): E23-37.
3. Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. *Am J Physiol Endocrinol Metab.* 2010; **298**(3): E449-66.
4. McBride J, Guest M, Scott E. The storage of the major liver components; emphasizing the relationship of glycogen to water in the liver and the hydration of glycogen. *J Biol Chem.* 1941; **139**: 943-52.
5. Aarsland A, Chinkes D, Wolfe RR. Hepatic and whole-body fat synthesis in humans during carbohydrate overfeeding. *Am J Clin Nutr.* 1997; **65**(6): 1774-82.
6. Acheson KJ, Schutz Y, Bessard T, Anantharaman K, Flatt JP, Jequier E. Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. *Am J Clin Nutr.* 1988; **48**(2): 240-7.
7. Hall KD. What is the required energy deficit per unit weight loss? *Int J Obes (Lond).* 2008; **32**(3): 573-6.
8. Chow CC, Hall KD. The dynamics of human body weight change. *PLoS computational biology.* 2008; **4**(3): e1000045.
9. Forbes GB. Lean body mass-body fat interrelationships in humans. *Nutr Rev.* 1987; **45**(8): 225-31.
10. Hall KD. Body fat and fat-free mass inter-relationships: Forbes's theory revisited. *Br J Nutr.* 2007; **97**(6): 1059-63.
11. Jackson AS, Stanforth PR, Gagnon J, Rankinen T, Leon AS, Rao DC, et al. The effect of sex, age and race on estimating percentage body fat from body mass index: The Heritage Family Study. *Int J Obes Relat Metab Disord.* 2002; **26**(6): 789-96.
12. Nelson KM, Weinsier RL, Long CL, Schutz Y. Prediction of resting energy expenditure from fat-free mass and fat mass. *Am J Clin Nutr.* 1992; **56**(5): 848-56.
13. Hall KD. Mathematical modelling of energy expenditure during tissue deposition. *Br J Nutr.* 2010; **104**(1): 4-7.
14. Blaxter K. *Energy metabolism in animals and man.* Cambridge: Cambridge University Press; 1989.
15. Hall KD, Jordan PN. Modeling weight-loss maintenance to help prevent body weight regain. *Am J Clin Nutr.* 2008; **88**(6): 1495-503.
16. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr.* 1990; **51**(2): 241-7.
17. Berlin NI, Watkin DM, Gevirtz NR. Measurement of changes in gross body composition during controlled weight reduction in obesity by metabolic balance and body density--body water technics. *Metabolism.* 1962; **11**: 302-14.
18. Heilbronn LK, de Jonge L, Frisard MI, DeLany JP, Larson-Meyer DE, Rood J, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *Jama.* 2006; **295**(13): 1539-48.
19. Runcie J, Hilditch TE. Energy provision, tissue utilization, and weight loss in prolonged starvation. *Br Med J.* 1974; **2**(5915): 352-6.

20. Hall KD, Guo J, Dore M, Chow CC. The progressive increase of food waste in America and its environmental impact. *PLoS One*. 2009; **4**(11): e7940.