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, 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 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. 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:

\[
\rho_G \frac{dG}{dt} = CI - k_G G^2
\]  

(1)

The parameter \( \rho_G = 17.6 \text{ MJ/kg} \) 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. 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.

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

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

(2)

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

\[ \rho_F \frac{dF}{dt} = \left(1 - p \right) \left( EI - EE - \rho_G \frac{dG}{dt} \right) \]
\[ \rho_L \frac{dL}{dt} = p \left( EI - EE - \rho_G \frac{dG}{dt} \right) \]  \hspace{1cm} (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 $\rho_F = 39.5 \text{ MJ/kg}$ and $\rho_L = 7.6 \text{ MJ/kg}$, 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. \(^11\)

\[ F_m = \frac{BW}{100} \left[ 0.14 \times age + 37.31 \times \ln \left( BW/H^2 \right) - 103.94 \right] \]
\[ F_w = \frac{BW}{100} \left[ 0.14 \times age + 39.96 \times \ln \left( BW/H^2 \right) - 102.01 \right] \]  \hspace{1cm} (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:

\[ EE = K + \gamma_F F + \gamma_L L + \delta BW + TEF + AT + \eta_L \frac{dL}{dt} + \eta_F \frac{dF}{dt} \]  \hspace{1cm} (5)

where $K$ is a constant determined by the initial energy balance condition, $\gamma_F = 13 \text{ kJ/kg/day}$ and $\gamma_L = 92 \text{ kJ/kg/day}$ are the regression coefficients relating resting metabolic rate versus body fat and lean mass, respectively. \(^12\) The parameters $\eta_F = 750 \text{ kJ/kg}$ and $\eta_L = 960 \text{ kJ/kg}$ account for the biochemical efficiencies associated with fat and protein synthesis \(^13\) 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:

\[ TEF = \beta_{TEF} \Delta EI \]  

(6)

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

\[ \tau_{AT} \frac{d\text{AT}}{dt} = \beta_{AT} \Delta EI - \text{AT} \]  

(7)

where \( \beta_{AT} = 0.14 \) was determined in our previous steady state analysis of longitudinal weight loss studies 15 and \( \tau_{AT} = 14 \) days sets the timescale for adaptive thermogenesis dynamics. 2, 3

The parameter \( \delta \) represents physical activity and a value of \( \sim 30 \) 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 \( \delta \) 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 \( \delta \) was then calculated as:

\[ \delta = \left[ (1 - \beta_{TEF}) \times \text{PAL} - 1 \right] \frac{\text{RMR}}{\text{BW}} \]  

(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 \( EE \):

\[ EE = \frac{K + \gamma_r F + \gamma_L L + \delta BW + TEF + AT + (EI - \rho_o dG/dt) \left[ \frac{p \eta_L}{\rho_L} + (1 - p) \eta_F / \rho_F \right]}{1 + p \eta_L / \rho_L + (1 - p) \eta_F / \rho_F} \]  

(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:

$$\frac{d\text{BW}}{dt} = \Delta EI - \frac{1}{(1-\beta)} \left[ \gamma_F + \alpha \gamma_L + \delta \right] (\text{BW} - \text{BW}_0)$$  \hspace{1cm} (10)

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

$$\rho \frac{d\text{BW}}{dt} = \Delta EI - \epsilon (\text{BW} - \text{BW}_0)$$ \hspace{1cm} (11)

where $\rho$ is an effective energy density associated with the BW change and $\epsilon$ is a parameter that defines how energy expenditure depends on BW:

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

and

$$\epsilon = \frac{1}{(1-\beta)} \left[ \gamma_F + \alpha \gamma_L + \delta \right].$$ \hspace{1cm} (13)

Therefore, the linearized equation can be written as:

$$\frac{d\text{BW}}{dt} = \Delta EI/\rho - (\text{BW} - \text{BW}_0)/\tau$$ \hspace{1cm} (14)

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

$$\tau = \frac{\eta_F + \rho_F + \alpha (\eta_L + \rho_L)}{\gamma_F + \delta + \alpha (\gamma_L + \delta)}$$ \hspace{1cm} (15)
Note that the physical activity parameter, \( \delta \), 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 \( \alpha = \frac{dL}{dF} \approx \frac{C}{F_0} \):

\[
\frac{\partial \tau}{\partial \alpha} = \frac{(\eta_L + \rho_L)(\gamma_F + \delta)}{[\gamma_F + \delta + \alpha(\gamma_L + \delta)]^2} \left( \frac{(\eta_F + \rho_F)(\gamma_L + \delta)}{[\gamma_F + \delta + \alpha(\gamma_L + \delta)]^2} \right)
\]  

(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 \( \tau \) with respect to \( \alpha \) is negative implying that the time constant increases for increasing body fat.

**Diet versus Physical Activity for Weight Loss**

At steady state, \( \frac{dF}{dt} = \frac{dL}{dt} = 0 \) and \( \Delta EE = \Delta EI \). Therefore, equation 11 can be solved for the eventual change of body weight, \( \Delta BW \):

\[
\Delta BW = \frac{(1 - \beta) \Delta EI - BW_{int} \Delta \delta}{\delta_{int} + \Delta \delta + \gamma_L - \Phi(\gamma_L - \gamma_F)}
\]  

(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 \( \Phi \) 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, \( \Delta \delta = \Gamma/\Delta BW_{int} \), where \( \Gamma \) 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:

\[
\Gamma = \frac{\beta}{1 - \beta} \left[ \delta_{int} + \Phi \gamma_F + (1 - \Phi) \gamma_L \right] BW_{int}
\]  

(18)

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

**References**


