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Basic nutritional investigation

New compartment model analysis of lean-mass and fat-mass growth with overfeeding

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ABSTRACT

Objectives: Mathematical models of lean- and fat-mass growth with diet are useful to help describe and potentially predict the fat- and lean-mass change with different diets as a function of consumed protein and fat calories. Most of the existing models do not explicitly account for interdependence of fat-mass on the lean-mass and vice versa. The aim of this study was to develop a new compartmental model to describe the growth of lean and fat mass depending on the input of dietary protein and fat, and accounting for the interdependence of adipose tissue and muscle growth.

Methods: The model was fitted to existing clinical data of an overfeeding trial for 23 participants (with a high-protein diet, a normal-protein diet, and a low-protein diet) and compared with the existing Forbes model.

Results: Qualitatively and quantitatively, the compartment model data fit was smoother with less overall error than the Forbes model. The root means square error were 0.39, 0.93 and 0.72 kg for the new model, the Forbes model, and the modified Forbes model, respectively. Additionally, for the present model, the differences between some of the coefficients (on the cross dependence of fat and lean mass as well as on the intake diet dependence) across different diets were statistically significant ($P < 0.05$).

Conclusions: Our new Dey-model showed excellent fit to overfeeding data for 23 normal participants with some significant differences of model coefficients across diets, enabling further studies of the model coefficients for larger groups of participants with obesity or other diseases.

Introduction

The high prevalence of overweight in the population has become increasingly important because overweight and obese individuals are susceptible to a number of diseases such as hypertension, diabetes, heart disease, and cancer [1,2]. Up to 69% of adults can be categorized as overweight; of these 35.1% are obese [3]. A properly organized diet can help to maintain a healthy weight and improve quality of life. To our knowledge, the significance of diet composition in response to overeating and energy dissipation in humans has not been well studied [4]. The effect of dietary protein on weight gain [5] was recently investigated in a controlled clinical study [6]. Overeating produced significantly less weight gain in individuals consuming a low-protein diet (LPD) than in individuals consuming a normal (NPD) or a high-protein diet (HPD).

This study is significant because the average daily diet for an individual is rarely balanced. Different foods and meals obviously contain different amounts of calories due to the various compositions of nutrients (fat, protein, carbohydrate). A mathematical model can be useful to generalize the results of the clinical trial and help to predict the effect of a particular

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diet on weight gain. The model can be important for certain cases where weight gain depends on diet only, without exercising. Also, existing models [6] that describe dependence of changes in the fat-free mass on the changes in fat mass do not explicitly take into account the interdependence of each of these independent energy reservoirs. We developed a compartment model with differential equations defining the change in lean and fat mass and their mutual dependence. In the present model, we consider the effect of dietary protein and fat consumption on lean- and fat-mass growth. The coefficients for the different terms of differential equation can be interpreted as a guide to which effects are stronger or weaker. We compared the present model performance on clinical data with that of the Forbes [6,7] model.

Background clinical study

The clinical study we are interested in was described previously [4]. Briefly, this was an overfeeding experiment conducted with 25 healthy, weight-stable individuals aged 18 to 35 y. Body mass index was between 19 and 30 kg/m^2. Three important characteristics of the protocol were measured frequently, which allows for modeling: body composition, resting energy expenditure, and total energy expenditure. Body composition was measured by dual x-ray absorptiometry and resting energy expenditure was measured by ventilated hood every 2 wk. Total energy expenditure was measured by double-labeled water before overeating, during a weight stabilization period and during the last week of the overfeeding paradigm.

Diet

After a weight stabilization period (13–25 d) at baseline, participants were randomly distributed to consume a diet that contained 5%, 15%, or 25% protein. Protein contribution to the diet defined LPD (5%), NPD (15%), and HPD (25%). Participants were overfed with the assigned diets for 8 wks. The metabolic kitchen prepared diets that were provided to participants in 5-d rotation with overfeeding calories prescribed in proportion to run-in energy requirement. A 5-d diet for each participant was prepared in duplicate, frozen, and prepared for the Covance Laboratories for protein, fat, and carbohydrate content analysis. Carbohydrate concentration was constant throughout the study. The chemical analysis showed that the LPD had 6% of energy from protein, 52% from fat, and 42% from carbohydrates. NPD had 15% of energy from protein, 44% from fat, and 41% from carbohydrates. HPD had 26% of energy from protein, 33% from fat, and 41% from carbohydrates.

Participants lived on the metabolic ward from the run-in period, through baseline testing and for the entire overfeeding period.

Number of participants

In all, there were 25 participants; 8 in each of the HPD and LPD groups and 9 in the NPD group. However, measured weight data were missing for one participant in the LPD group and one in the NPD group; hence they were eliminated from analysis.

Background on existing mathematical model

Different existing models explore the dependence of energy expenditure and fat mass [5]. The Hall model consists of two differential equations that describe dependence of the body composition change depending on the energy expenditure and storage of glycogen.

$$\rho_F \frac{dF}{dt} = (1-p)\left(EI - EE - \rho_G \frac{dG}{dt}\right) \quad (1)$$

$$\rho_L \frac{dL}{dt} = p\left(EI - EE - \rho_G \frac{dG}{dt}\right) \quad (2)$$

In formulas 1 and 2 ρ_L, ρ_F represent the energy content per unit change of body lean and fat masses, ρ_G represents the energy density of glycogen, EI is energy intake and EE is energy expenditure, G is the glycogen intake, p is partitioning function (detailed description in the original paper [5]).

However, the present experimental data from the overfeeding study [4] does not have the information about the amount of energy expenditure and change in glycogen.

The Forbes model [6,7] was introduced as a model for predicting individual weight change in humans.

$$FFM(t) = 10.4 \ln\left(\frac{F(t)}{D}\right) \quad (3)$$

FFM is fat-free mass and F is a fat mass. We used the Forbes model to compare to our model predictions. Fat mass was

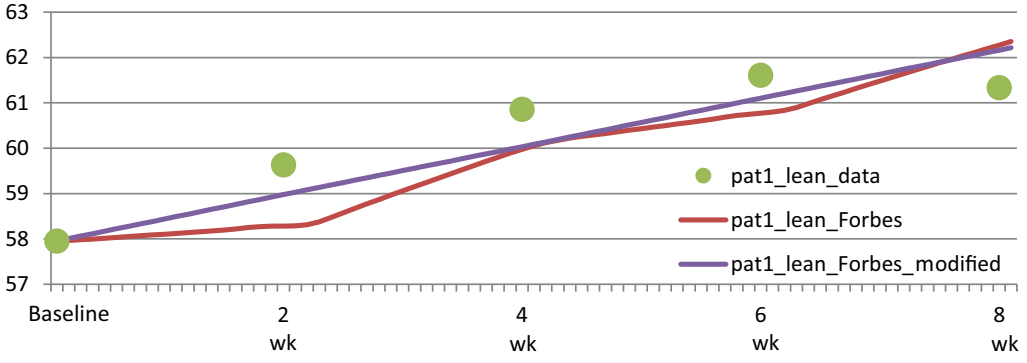

Fig. 1. Lean mass of participant 1 change with a high-protein diet, fitted to Forbes and modified Forbes models.

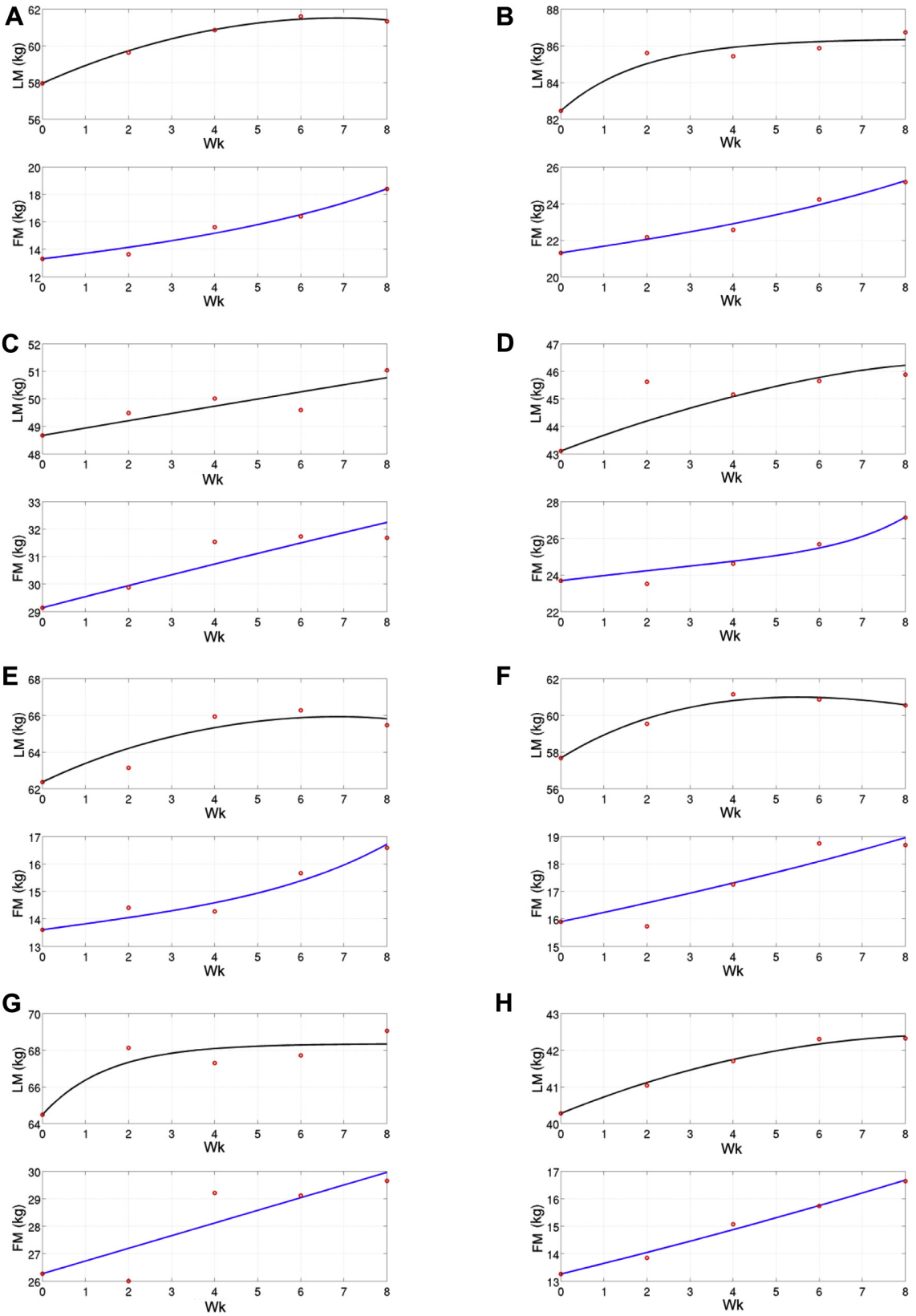

Fig. 2. New Model fitted to HPD (high-protein diet): lean (LM) and fat (FM) masses change for eight participants (A-H). O-rings represent original data. FM, fat mass; LM, lean mass.

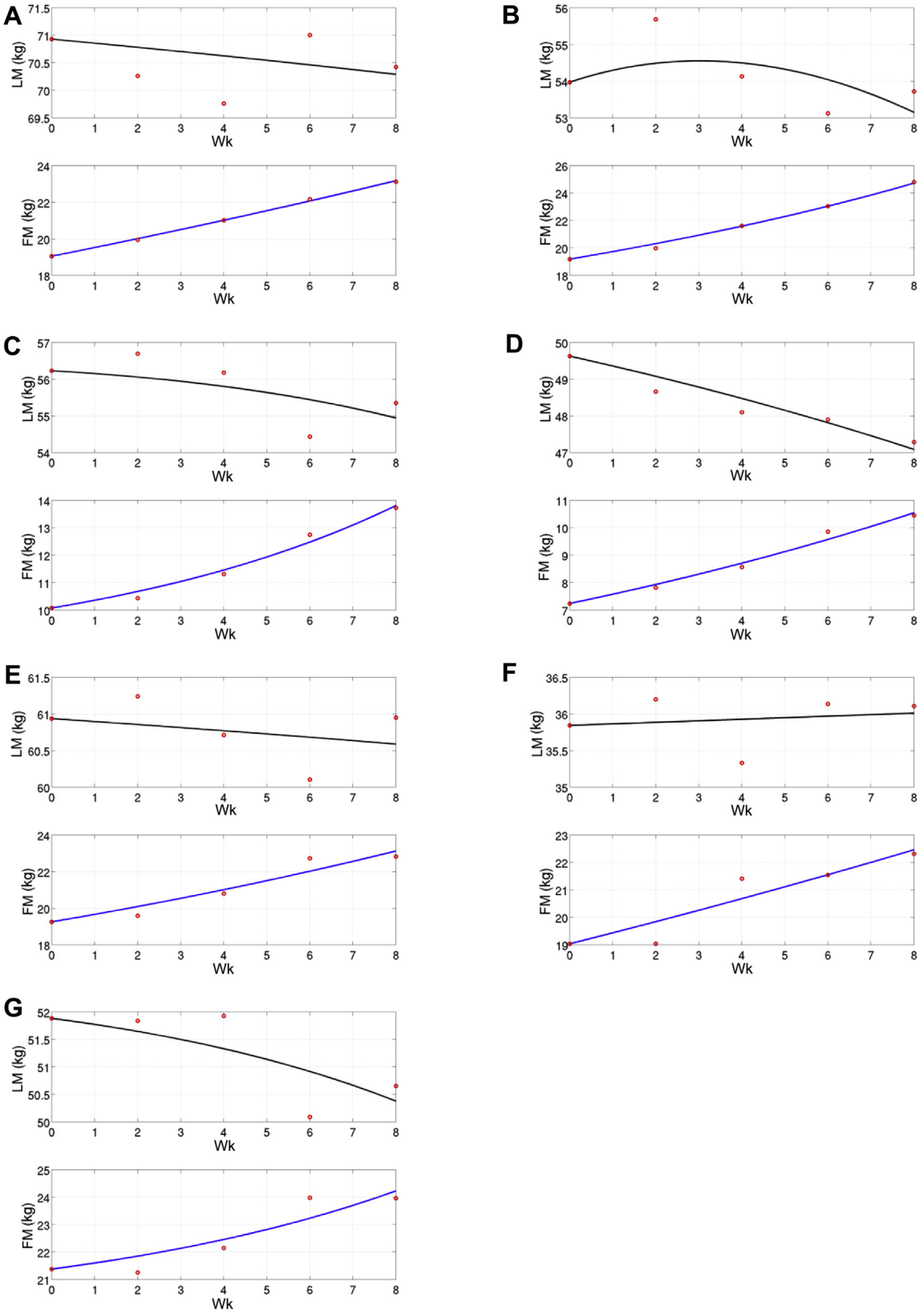

Fig. 3. New Model fitted to LPD (low-protein diet lean): (LM) and fat (FM) masses change for seven participants (A-G). O-rings represent original data.

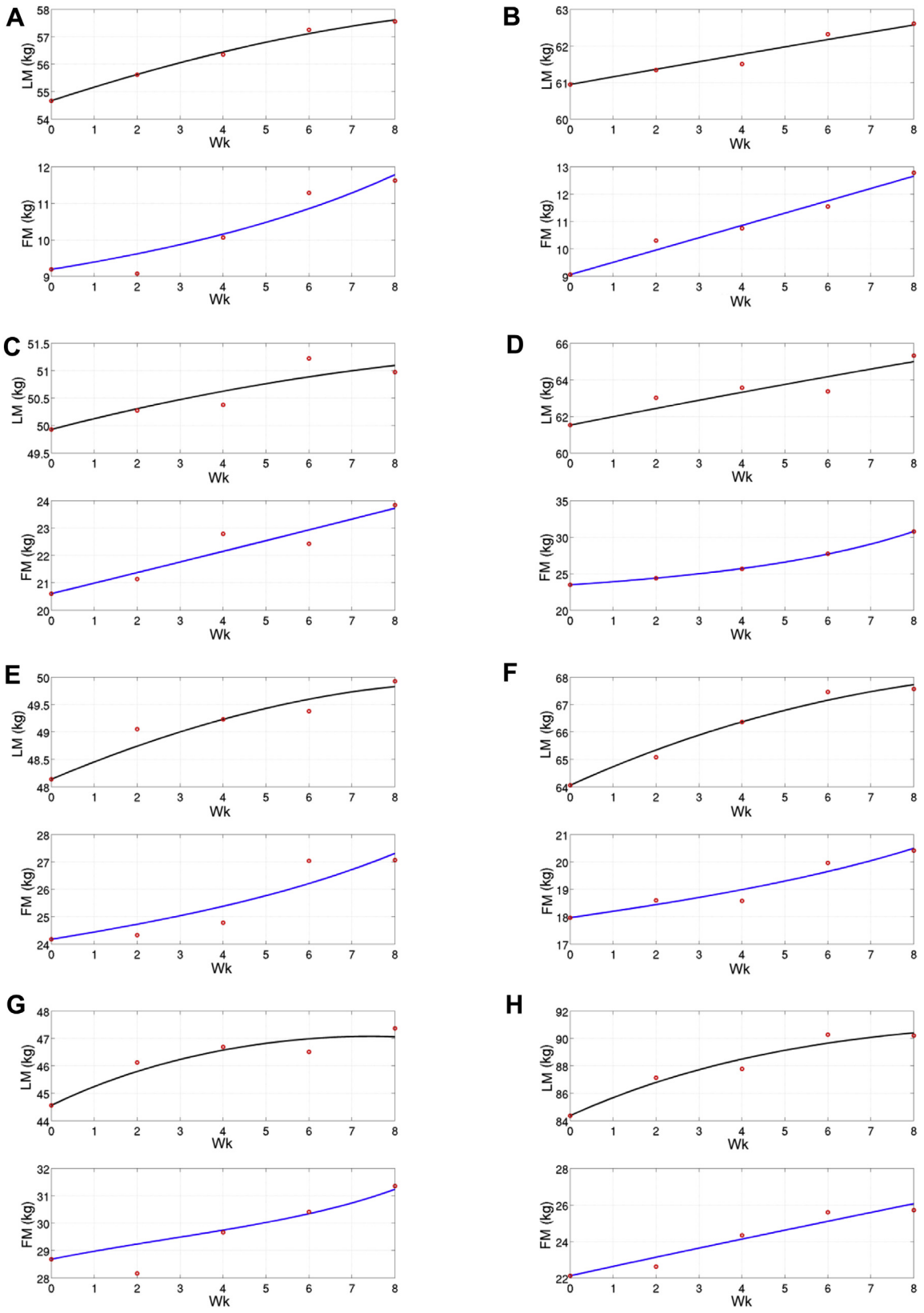

Fig. 4. New Model fitted to NPD (normal-protein diet): lean (LM) and fat (FM) masses change for eight participants (A-H). O-rings represent original data.

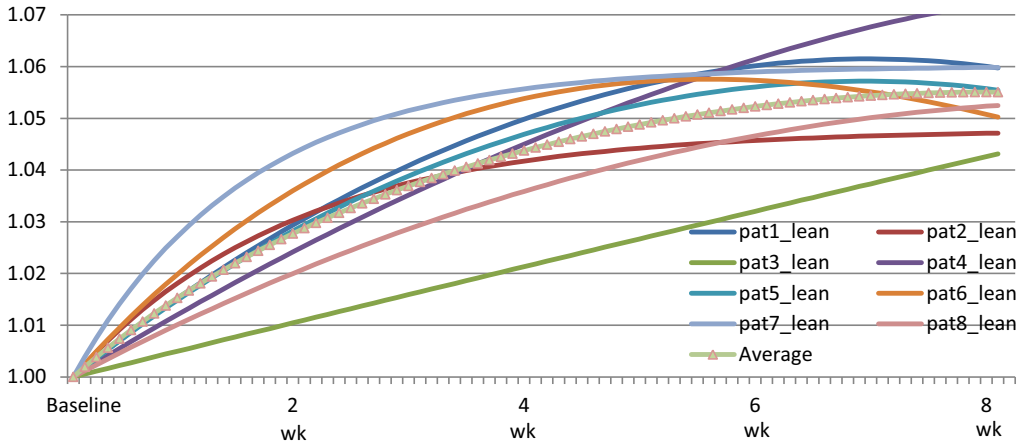

Fig. 5. Lean-mass change during the overfeeding period of high-protein diet.

directly obtained in the clinical experimental data, whereas fat-free mass change with time was simulated and fitted to experimental data.

Before curve fitting, the equation was differentiated. As stated in the original paper, the constant of 10.4 shown in the Eq. 3 was used for males, whereas a constant of 13.8 was used for females. We decided to treat this constant as a variable coefficient termed "aa" because we had both male and female participants in our overfeeding study. After differentiation, the equation is simplified as:

$$\frac{dFFM}{dt} = \frac{(aa/D)}{F}\frac{dF}{dt} \tag{4}$$

Where *aa* is the variable that was marked 10.4, and *D* is the same as in Eq. (3). In a modified version of Forbes model (detailed in Results section) a constant was added.

Methods

New compartmental model

We introduced a system of differential equations (formulated by author J.D.) that represent body composition as a function of protein and fat content in diets as the following:

$$\frac{dL}{dt} = a_i I_p(1 - L/c) - a_i F \tag{5}$$

$$\frac{dF}{dt} = a_f I_f F + a_2 I_f - b_f L \tag{6}$$

Variables L and F stand for the lean and fat masses, respectively. Coefficients a_i, a_f, b_f, a_1, and c stand for the rates of different processes that take place during the weight accumulation and lean- and/or fat-mass formation. Constants I_p and I_f are daily values (in kg) of protein and fat inputs.

Our model is based on a macroscopic description. The heuristic rationale for this model is as follows: the diet-dependent component of the change in the lean mass is assumed to be primarily on protein intake (in a linear exponential fashion). The lean mass growth, however, is impeded by the fat mass. The fat mass is primarily related to the fat input in diet (linear exponentially) and impeded by the lean mass.

For the input protein/fat dependence, we found it adequate to keep linear exponential terms with rising (and/or asymptotically saturating) dependencies. For fat mass this yielded $\frac{dF}{dt} = a_f I_f F + a_2 I_f$ and for lean mass, an exponentially saturating dependence $\frac{dL}{dt} = a_i I_p(1 - L/c)$. In the latter, linear exponential coefficients were simply rearranged such that c is an interesting "virtual" lean mass (in kg) to which the lean mass would have asymptotically approached on protein feeding if the lean mass was not impeded by the fat mass.

Note that other terms could be added such as growth of lean-mass dependence on input fat I_f but the current model was found adequate as a first-approximation compartmental model. The important part of our model is to take care of the interdependencies of the changes in *F* and *L*.

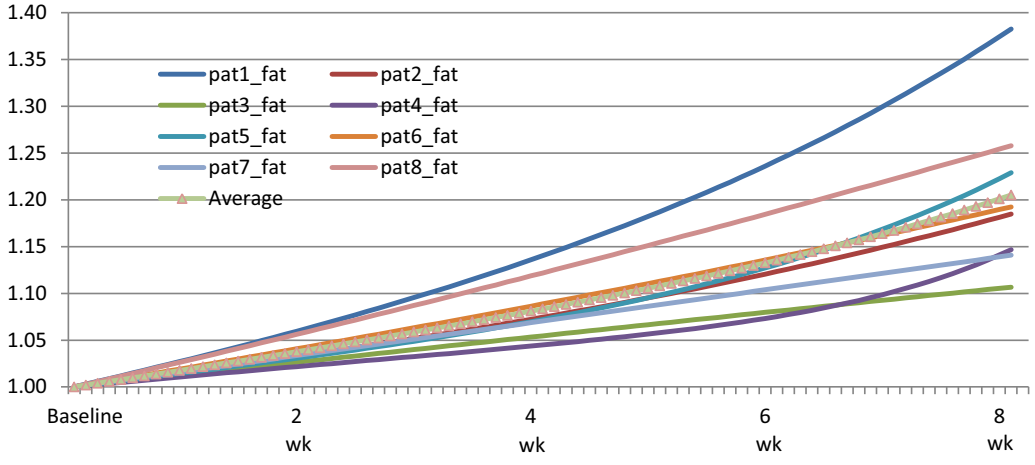

Fig. 6. Fat-mass change during the overfeeding period of high-protein diet.

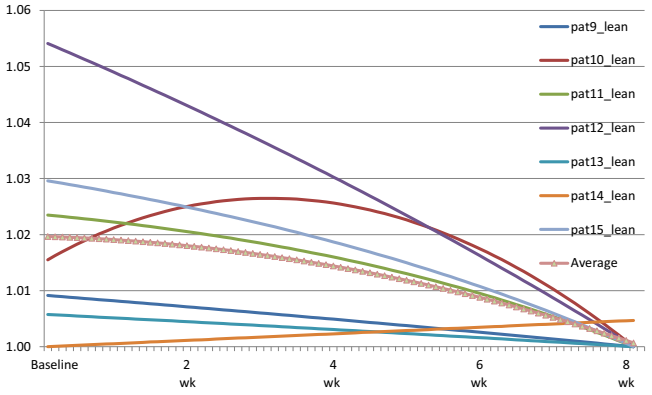

Fig. 7. Lean-mass change during the overfeeding period of low-protein diet.

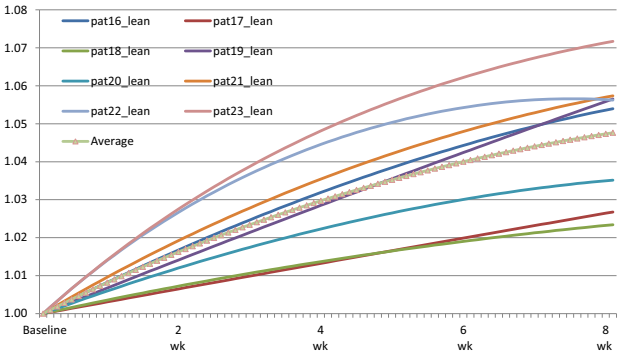

Fig. 9. Lean-mass change during the overfeeding period of normal-protein diet.

Even though out of scope of this study, some of these parameters may be particularly important for participants with obesity. For example b_f may change sign as there is evidence of significant conversion of lean mass into fat mass [8,9], particularly for overweight or obese patients.

Data fitting

Data fitting was performed in Matlab with help of ode45 differential equation solver and *fmincon* minimization routine. The quality of fit was judged with help of χ^2 analysis. The coefficients for the LPD, NPD, and HPD were considered two at a time to test for statistically significant differences.

Results

Fitting to the Forbes model

Figure 1 shows the fit of lean mass for the first participant on the HPD diet according to the Forbes model. The points represent the experimental results and the curve represents the model fit. For most participants, the curve fit was not smooth—although the output masses themselves were continuous, some of them had discontinuous slopes. Quantitatively, the error sum of squares (SSE) or the χ^2 error was relatively high, with overall average (overall data points for all 23 participants) error being 0.86 kg^2 with root mean squared error (RMSE) as 0.93 kg. We modified the model to add a linear term (ie, a constant *cc* for the differential), shown in Eq. 7. Qualitatively, the fit was improved for many cases (including participant 1; see Fig. 1) for the modified Forbes model, but many still had some discontinuities in slope.

$$\frac{dFFM}{dt} = \frac{(aa/D)}{F}\frac{dF}{dt} + cc \tag{7}$$

As illustrated in Figure 1, application of the modified Forbes model did not significantly improve the quality of the fit. Quantitatively the average SSE for all participants (across all diets) was 0.51 kg^2 and the RMSE was 0.72 kg. Finally, we used our newly introduced model for data fitting and compared the solution quantitatively and qualitatively to both the Forbes and the modified Forbes models.

Data fitting to new model

As shown in Figures 2 to 4, the fitting of our model to the HPD, LPD, and the NPD data for the participants was excellent (and smooth), particularly for the lean mass. The ranges of mass growth for the three diets are different; hence the displayed scales for the three diets are different, for best visualization.

To appreciate the results of lean and fat mass for all participants, we normalized the values according to the minimum (starting or ending) value for each individual for the different diets. For most cases, the starting data value was chosen for normalization; however, some masses had a falling trend so we

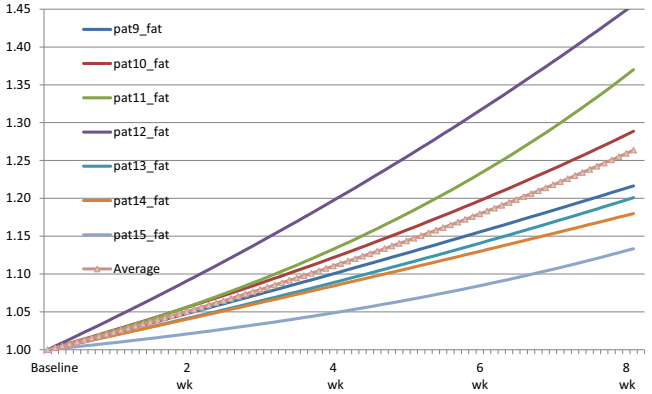

Fig. 8. Fat-mass change during the overfeeding period of low-protein diet.

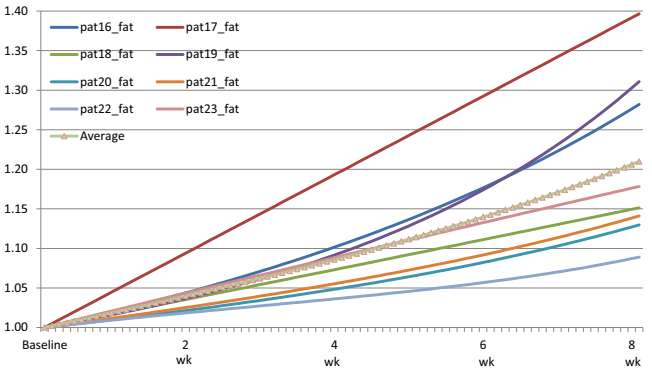

Fig. 10. Fat-mass change during the overfeeding period of normal-protein diet.

Table 1
Fitted parameters for different participants and different diets, SSE of the fitting procedure

Participant	Diet	a_i	c	a_f	b_f	b_i	a_1	a_2	SSE kg^2
1.00	HPD	40.24	91.90	1.25	0.03	0.01	0.18	0.41	0.05
2.00	HPD	203.38	86.36	1.00	0.03	0.01	0.00	3.29	0.11
3.00	HPD	2.60	90.20	0.00	0.10	0.01	0.00	40.00	0.14
4.00	HPD	70.76	93.03	2.76	0.19	0.01	0.32	0.00	0.18
5.00	HPD	63.12	90.52	2.13	0.06	0.01	0.25	1.56	0.21
6.00	HPD	83.70	96.73	0.34	0.01	0.01	0.39	0.00	0.14
7.00	HPD	315.59	72.23	0.00	0.00	0.01	0.14	3.56	0.49
8.00	HPD	14.16	90.07	0.18	0.00	0.01	0.10	0.69	0.01
9.00	LPD	0.00	90.00	0.13	0.00	0.01	0.00	0.03	0.14
10.00	LPD	21.33	90.13	0.36	0.02	0.01	0.19	1.39	0.29
11.00	LPD	3.39	90.03	0.69	0.02	0.01	0.07	0.76	0.19
12.00	LPD	0.00	90.01	0.29	0.00	0.01	0.04	0.79	0.05
13.00	LPD	0.00	89.99	0.25	0.01	0.01	0.00	0.10	0.15
14.00	LPD	0.07	90.00	0.11	0.00	0.01	0.00	0.11	0.17
15.00	LPD	13.94	90.15	0.53	0.04	0.01	0.13	1.57	0.22
16.00	NPD	23.26	90.05	0.86	0.02	0.01	0.08	0.10	0.06
17.00	NPD	4.68	90.01	0.00	0.00	0.01	0.00	2.44	0.03
18.00	NPD	12.89	90.23	0.03	0.00	0.01	0.03	1.59	0.09
19.00	NPD	10.75	89.92	1.41	0.09	0.01	0.00	0.05	0.12
20.00	NPD	26.87	90.90	0.93	0.09	0.01	0.06	2.03	0.14
21.00	NPD	50.55	90.10	0.98	0.05	0.01	0.07	0.01	0.05
22.00	NPD	86.96	92.18	1.42	0.16	0.01	0.19	0.00	0.16
23.00	NPD	105.81	107.06	0.00	0.01	0.01	0.08	7.50	0.17
									Average = 0.15

HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet; SSE, error sum of squares

had to normalize the data to the final data value to visualize the trend. Normalized curves for the lean- (Figs. 5 and 6) and fat-mass (Figs. 7 and 8) changes during HPD similarly showed the normalized curves of the fitted model to lean mass and fat mass, for the LPD group. Figures 9 and 10 show the corresponding results for NPD. The normalized models in Figures 5 and 9 show a consistent pattern across participants in the HPD or NPD groups. For these groups, lean mass grew and then saturated or fell (presumably due to the weight of the rising fat mass), whereas for the LPD (Fig. 7) the lean mass actually decreased from the onset of the diet. The fat masses appeared to rise for all groups in a linear exponential pattern (Figs. 6, 8, and 10).

Table 1 shows the parameters that were obtained after fitting the clinical data to the introduced model. It also shows the SSE (ie, the χ^2 as a quality of fit judgment for overall mass, fat mass, and lean mass). For each participant, the SSE shown was the average over the 5 data points. The average SSE (over all data points and participants) was 0.15 kg^2 and the RMSE was 0.39 kg.

Figures 11 to 16 are bar plots that show the average fit of coefficients for each diet group. The statistical differences between rate coefficients of our equation across the different diets were tested using a Student's t test because there was no explicit dependence between coefficients. We discuss the coefficients as they appear in Eqs. 5 and 6 and the results are summarized in Table 2.

For the LPD, we observed that a_i was low, indicating that the linear exponent protein-intake dependence was low for LPD. For HPD or NPD, a_i was several factors higher and statistically significant from LPD ($P < 0.05$).

The coefficient a_1 indicating the effect of the fat-mass on lean-mass growth was significantly higher for HPD compared with NPD or LPD ($P < 0.05$). The coefficient was similar for NPD and LPD.

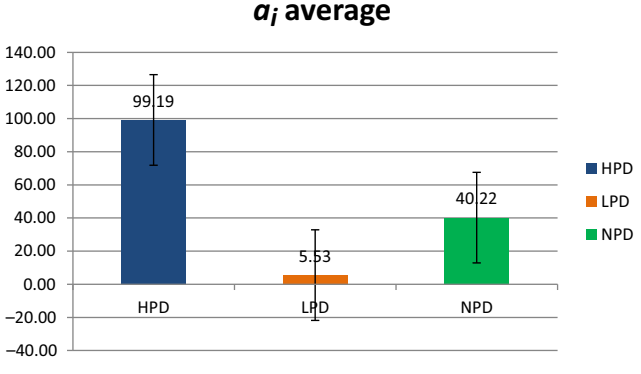

Fig. 11. Average a_i coefficient with standard error for different type of diets. HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet.

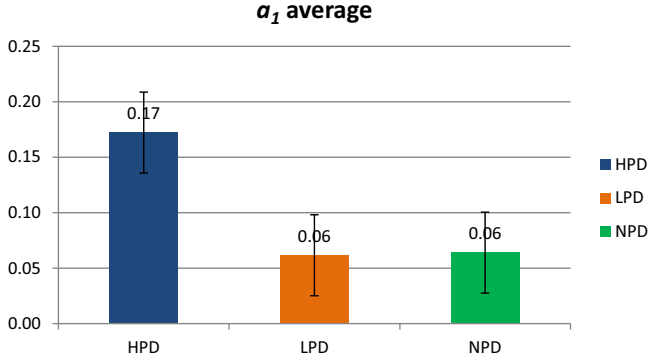

Fig. 12. Average a_1 coefficient with standard error for different type of diets. HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet.

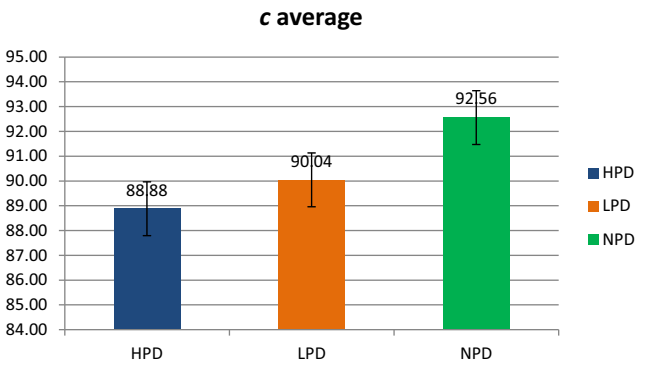

Fig. 13. Average c coefficient with standard error for different type of diets. HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet.

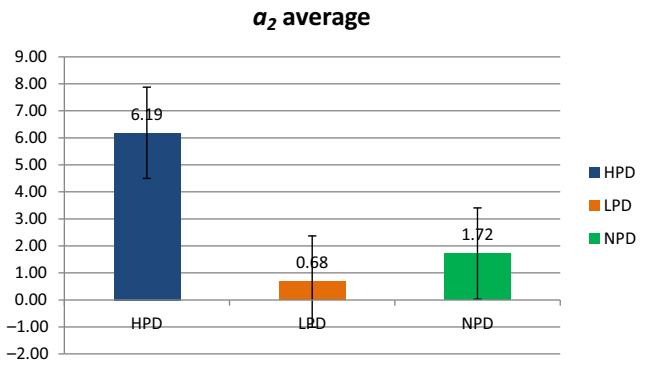

Fig. 15. Average a_2 coefficient with standard error for different type of diets. HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet.

The coefficient c is an interesting quantity that can be possibly called the "virtual" unimpeded lean mass. As shown in the figures and in Table 1, we observed that coefficient c was very similar for all participants across diets, hovering tightly around 90 kg. The average for HPD was slightly lower but there was no statistically significant difference across the different diets.

Of the coefficients in Eq. 6, b_f was similar on the average between HPD and NPD but about five times lower in the LPD. However, the difference was not statistically significant (although LPD–NPD was border line at 0.05). Coefficients a_2 and a_f did not show statistically significant differences.

In summary, a few coefficients may be of interest as discriminatory across diet groups such as a_i (protein-intake dependence), a_1 (determining effect of fat mass on lean-mass growth), and possibly b_f (determining effect of lean mass on fat-mass growth). Of the three coefficients (a_i, a_f, a_2) determining the input diet dependence on lean-mass or fat–mass change, the coefficient a_i (protein-intake dependence) was significantly different for the LPD. The coefficient c (can be described as the "virtual unimpeded lean mass") was remarkable in having similar value across all the 23 participants regardless of diet.

The percent change in lean and fat mass for each participant based on the model can be found in Table 3. During overeating of the HPD, increase in the lean mass was 6% and fat 20%. During overeating LPD, lean mass decreased ~1%, but fat increased by 26%. During the NPD, lean mass increased by 5% and fat increased by 21%.

Discussion

Daily consumption of different amounts of protein and fat during an overfeeding diet with constant carbohydrate consumption can cause growth of the extra fat or lean mass, or both.

In our research, we interpreted existing clinical data from a controlled overfeeding study [4] using a newly introduced mathematical model. Data reflects the weight change in the condition of normal diet and overfeeding with protein or fat. Our mathematical model for the description of the weight change involved extra coefficients to describe cross-dependence of fat and lean mass that takes place during consumption of certain macronutrients. Results of this study can help in predicting the weight change for individuals making particular diet adjustments.

The clinical study [4] was an expensive project (~$10 million) involving close monitoring of participants with an extended stay on a metabolic ward. Thus number of participants in each diet group was relatively small (n = 7–8), however, this was a state-of-the-art controlled clinical trial and

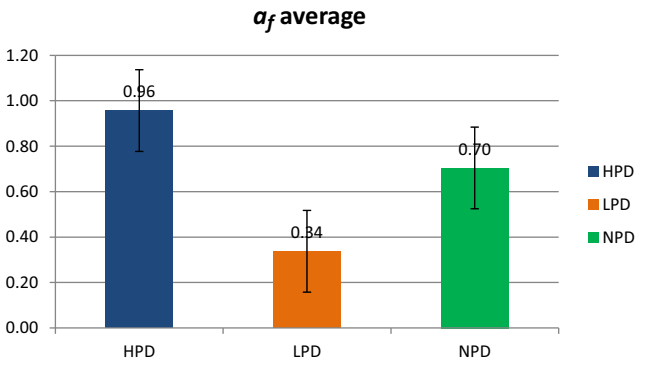

Fig. 14. Averaged a_f coefficient with standard error for different type of diets. HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet.

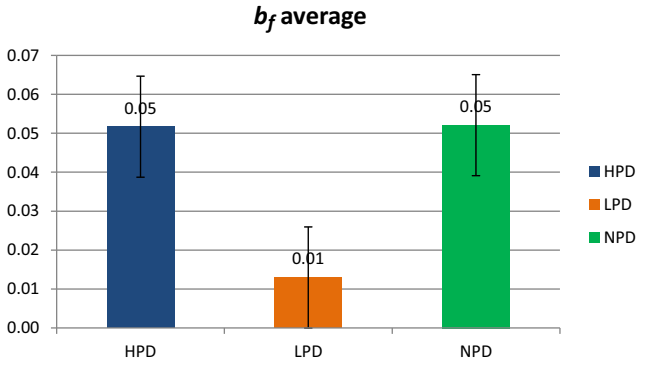

Fig. 16. Average b_f coefficient with standard error for different type of diets. HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet.

Table 2
Student's *t* Test for Same Sets of Coefficients

Diet significance	a_i	a_1	c	a_f	a_2	b_f
HPD–LPD	0.02	0.04	0.34	0.07	0.16	0.07
LPD–NPD	0.02	0.47	0.14	0.08	0.16	0.05
NPD–HPD	0.08	0.03	0.14	0.28	0.19	0.49

HPD, high-protein diet; LPD, low-protein diet; NPD, normal protein diet

hence the data are hugely valuable for the testing and generation of new mathematical models of weight and body composition changes.

In our analysis for the data fitting and the resulting SSE (χ^2 analysis) we have 5 data points (over 8 wk) for each participant. Thus the overall SSE or χ^2 error value is $>23 \times 5 = 115$ data points and therefore we expect our model-fitting results to translate well to a larger population.

For the statistical analysis of coefficients the sample size was smaller (n = 7–8) for each diet group but within this limitation we found some coefficients that may help to discriminate across different diets. These are the coefficients of cross dependence of fat and lean mass on their respective growth and not explicitly considered in other models in the literature. For example, the coefficient b_f describes dependence of the fat mass on the lean mass. It was similar for both the HPD and NPD, but much smaller (about five times) on the average for the LPD. The a_1 and b_f potentially may have significance in investigating weight change for diseased patients such as those with obesity or diabetes. Additionally, the finding of a near-constant (across all 23 participants, regardless of diets) "virtual unimpeded lean mass" (coefficient c) was a significant finding of this study.

There is almost no dependence of the lean-mass increase based on the initial lean mass, achieved during weight stabilization period. Lean mass experienced a decrease during the LPD (~1%), its effect on the fat-mass change is more efficient.

The new model takes into account more realistic interdependencies between lean and fat mass than the Forbes model and the better quality of fit suggests that it is expected to be more precise in the clinic. The software is currently research grade but uses standard ode-solver packages. We started from zero initial conditions for all 23 participants and the results converged in the minimizer. In the future, the software may be made more user-friendly with a GUI-based interface and expected to straightforwardly translate into the clinic.

As mentioned previously, the patient data in this study is expensive to acquire and thus is limited and that in part makes the data set unique. The model-fitting error was lower than Forbes model for 23 data sets. The mathematical model presented here may therefore be useful in generalizing the results of the clinical trial and helping in prediction of fat- and lean-mass growth. The dietary subgroups are smaller (seven to eight data sets each), so to make significant conclusions about the output coefficients within each dietary subgroup, larger numbers of samples are necessary to be acquired and studied in the future.

Table 3
Fat and lean mass percent change as a result of HPD, LPD, and NPD consumption

Participant	Diet	FM increase (%)	Average FM increase (%)	LM increase (%)	Average LM increase (%)
1	HPD	38	20	6	6
2	HPD	18		5	
3	HPD	9		5	
4	HPD	15		6	
5	HPD	22		5	
6	HPD	18		5	
7	HPD	13		7	
8	HPD	26		5	
9	LPD	21	26	−1	−1
10	LPD	29		0	
11	LPD	36		−2	
12	LPD	44		−5	
13	LPD	19		0	
14	LPD	17		1	
15	LPD	12		−2	
16	NPD	26	21	5	5
17	NPD	41		3	
18	NPD	16		2	
19	NPD	31		6	
20	NPD	12		4	
21	NPD	14		5	
22	NPD	9		6	
23	NPD	16		7	

FM, fat mass; HPD, high-protein diet; LM, lean mass; LPD, low-protein diet; NPD, normal protein diet

Conclusion

We have a new parsimonious compartmental model to describe the growth of lean and fat mass depending on protein and fat content of the diet. The model fit was excellent on existing overfeeding data for 23 participants with diets of different protein content. Quantitatively using the χ^2 measure (SSE), the quality of fit was better for the newly introduced model when compared with the existing and a modified Forbes model. The RMSEs were 0.39, 0.93, and 0.72 kg, respectively for the new model, Forbes model, and the modified Forbes model. Importantly, our Dey-model is not too complex to be efficiently used for potential prediction of the change in fat and lean masses depending on the diet, thus giving a prediction of the change in body composition. Additionally, we observed that some coefficients describing the cross dependence of fat and lean mass as well as describing the intake diet dependence are significantly different across the different diets (within our constraints of small sample sizes of seven to eight data sets). Studying these coefficients for patients with obesity or other diseases and comparing with normal participants for normal or modified diets for larger sample sizes may be of interest for nutrition scientists, biologists and biophysicists.

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