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Computer Modeling of Obesity Links Theoretical Energetic Measures with Experimental Measures of Fuel Use for Lean and Obese Men[1]

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Abstract

The goal of this research was to use a computational model of human metabolism to predict energy metabolism for lean and obese men. The model is composed of 6 state variables representing amino acids, muscle protein, visceral protein, glucose, triglycerides, and fatty acids (FAs). Differential equations represent carbohydrate, amino acid, and FA uptake and output by tissues based on ATP creation and use for both lean and obese men. Model parameterization is based on data from previous studies. Results from sensitivity analyses indicate that model predictions of resting energy expenditure (REE) and respiratory quotient (RQ) are dependent on FA and glucose oxidation rates with the highest sensitivity coefficients (0.6, 0.8 and 0.43, 0.15, respectively, for lean and obese models). Metabolizable energy (ME) is influenced by ingested energy intake with a sensitivity coefficient of 0.98, and a phosphate-to-oxygen ratio by FA oxidation rate and amino acid oxidation rate (0.32, 0.24 and 0.55, 0.65 for lean and obese models, respectively). Simulations of previously published studies showed that the model is able to predict ME ranging from 6.6 to 9.3 with 0% differences between published and model values, and RQ ranging from 0.79 to 0.86 with 1% differences between published and model values. REEs >7 MJ/d are predicted with 6% differences between published and model values. Glucose oxidation increases by ~0.59 mol/d, RQ increases by 0.03, REE increases by 2 MJ/d, and heat production increases by 1.8 MJ/d in the obese model compared with lean model simulations. Increased FA oxidation results in higher changes in RQ and lower relative changes in REE. These results suggest that because fat mass is directly related to REE and rate of FA oxidation, body fat content could be used as a predictor of RQ. J. Nutr. 144: 1650–1657, 2014.

Introduction

Using a systems approach to understand mechanisms involved in obesity allows researchers to focus on the most quantitatively important information and predict individual responses to changes in physiologic states. Obesity is not only associated with changes in diet and body composition but also changes in fuel use, resting energy expenditure (REE),[4] heat production, organ size, etc. (1). The systems approach, which allows for interactions between subsystems and their environment input and output, is ideal for examining obesity because diet, energy expenditure, energy production, fuel use, and underlying metabolic processes such as protein synthesis and fat metabolism can be represented mathematically to identify differences in intake, metabolism, and excretion in lean and obese men. Sensitivity analyses can then be used to quantify the relative importance of these factors and processes (intake, fuel use) to metabolic changes associated with obesity. Understanding changes that occur with obesity is important to understand why individuals are metabolically different. For instance, the Harris-Benedict equations are used to predict REE based on parameters such as body weight (BW), age, and sex. But the best a regression line can do is predict the mean REE. Many points or REEs for individuals will not fall on the line, meaning that for the same BW, for instance, individuals can have very different

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[4] Abbreviations used: Aa, amino acids; AaAc, amino acid degradation to acetyl CoA; AaCd, amino acid oxidation rate (in mol/d); AaCdATP, ATP production from oxidation of amino acids (in mol/d); AaCdOx, oxygen used from amino acid oxidation (in mol/d); AaGl, glucose production from glucogenic amino acids (in mol/d); AaPb, amino acids incorporated into muscle protein (in mol/d); AaPbADP, ADP production from body protein synthesis (in mol/d); AaPl, long turnover protein pool synthesis (in mol/d); AaPlADP, ADP production from protein synthesis of long turnover proteins (in mol/d); AaPv, amino acids incorporated into visceral protein (in mol/d); AaPvADP, ADP production from protein synthesis of visceral protein (in mol/d); AaUr, urea synthesis (in mol/d); AaUrADP, ADP production from urea synthesis (in mol/d); Abs, absorbed; AbsAa, absorbed amino acid (in mol/d); AbsAaADP, ADP production from cost of amino acid absorption (in mol/d); AbsGl, absorbed glucose (in mol/d); AbsGlADP, ADP production from cost of glucose absorption (in mol/d); AbsTg, absorbed TG (in mol/d); AbsTgADP, ADP production from cost of TG absorption (in mol/d);

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REEs. By using the systems approach, many more factors can be used and examined through sensitivity analyses to determine their role in obesity rather than using linear approximations of REE based on BW, age, and sex.

Computer modeling based on metabolic mechanisms is a useful tool for the systems approach to challenge existing theories, find gaps in knowledge, explain phenomena, predict responses, develop weight management strategies, and "simulate" experiments by using different experimental designs. Computer modeling provides a unique method to assess what is known about obesity and metabolism and explores what metabolic effects (diet, exercise, body composition, mitochondrial energy spilling, protein turnover, etc.) have on BW. Mechanistic computer models have been used successfully to predict nutrient requirements for lactating cattle (2), to predict growth (3), and to understand organ metabolism (4). Therefore, it is possible to represent nutrient metabolism and simulate metabolic function by using mechanistic computer models. The objectives of this study are to describe mechanistic computer models of lean and obese humans based on energy metabolism and use sensitivity analyses and literature data with model simulations to explore the effects of changes in BW, composition, diet, and metabolism on energy metabolism. Sensitivity analysis will be used to determine the relevance of the mathematical representation, and model simulation of different metabolic states (changes in protein turnover, diet and body composition, and metabolic flexibility) will be used to understand why energy requirements, predicted metabolizable energy (ME), REE, respiratory quotient (RQ), phosphate to oxygen ratio (PO), glucose oxidation rate (GlCd), and FA oxidation rate (FaCd) are different in lean and obese individuals.

Ac, acetyl CoA (in mol); AcCd, acetyl CoA oxidation (in mol/d); AaCdATP, ATP production from amino acid oxidation (in mol/d); AcFa, FA synthesis; AcFaADP, ADP production from FA synthesis from acetyl CoA (in mol/d); AcHy, production of NADPH from acetyl CoA (in mol/d); AcHyADP, ADP from production of NADPH from malic enzyme (in mol/d); ADP, high-energy phosphate bond used (in mol); Ag, α glycerol phosphate; AtAdHt, heat produced as a result of ATP use; ATP, high-energy phosphate bond (produced) (in mol); ATPADP, ADP produced from ATP (in mol/d); BasalP, Basal ATP used based on metabolic body size (in mol/d); BW, body weight; Cd, carbon dioxide (in mol); cFa, blood concentration of FAs; cGl, blood concentration of glucose; CHO, percentage of carbohydrate in the diet; cNADH, cytoplasmic NADH (in mol); dPb, change in body protein (in mol/d); dPl, change in long turnover protein (in mol/d); dPv, change in visceral protein (in mol/d); dTs, change in storage TG (in mol/d); durea, urea produced (in mol/d); EB, energy balance; EBB, energy balance body; FaCd, FA oxidation rate (in mol/d); FaCdATP, ATP production from oxidation of FAs (in mol/d); FaCdCd, carbon dioxide produced from FA oxidation (in mol); FaCdOx, oxygen used in FA oxidation (in mol); FaTs, FAs incorporated into storage TG (in mol/d); FaTsADP, ADP production from storage TG synthesis from FAs (in mol/d); FdIE, ingested energy intake; FFM, fat-free mass; FeNRG, fecal energy; FSR, fractional protein synthesis rate; F6P, fructose 6 phosphate (in mol); F6PAc, fructose 6 phosphate degradation to acetyl CoA (in mol/d); F6PAcADP, ADP production from fructose 6 phosphate conversion to acetyl CoA; Gl, glucose (in mol); GlAa, amino acid synthesis from glucose (in mol/d); GlAc, rate of glucose conversion to acetyl CoA for FA synthesis (in mol/d); GlAcATP, ATP from production of acetyl CoA production from glucose (in mol/d); GlAcOx, oxygen used in production of acetyl CoA production from glucose (in mol/d); GlAg, α glycerol phosphate from glucose (in mol/d); GlAgADP, ADP production from glucose conversion to α glycerol phosphate (in mol/d); GlCd, glucose oxidation rate (in mol/d); GlCdATP, ATP production from oxidation of glucose (in mol/d); GlCdCd, carbon dioxide produced from glucose oxidation (in mol/d); GlCdOx, oxygen used in glucose oxidation (in mol/d); GlHy, rate of production of NADPH from glucose passing through pentose phosphate path (in mol/d); GlHyADP, ADP from production of NADPH from glucose (pentose phosphate) (in mol/d); GlHyCd, carbon dioxide produced from NADPH production from glucose (in mol/d); GlLa, lactate production from glucose (in mol/d); GlLaATP, ATP from production of glucose from lactate (in mol/d); Gy, glycerol (in mol); GyCd, glycerol oxidation rate (in mol/d); GyCdATP, ATP produced from glycerol production (in mol/d); GyCdCd, carbon dioxide produced from glycerol oxidation (in mol/d); GyCdOX, oxygen used from glycerol oxidation (in mol/d); GyGl, glucose production from glycerol (in mol/d); GyGlADP, ADP production from glycerol conversion to glucose (in mol/d); G3P, glyceraldehyde 3 phosphate (in mol/d); G3PAc, glycerol 3 phosphate degradation to acetyl CoA (in mol/d); G3PAcADP, ADP production from glyceraldehyde 3 phosphate conversion to acetyl CoA (in mol/d); Hc, heat of combustion; HcPb, heat of combustion of protein; HcTg, heat of combustion of TG; Heart, ATP use for heart work (in mol/d); HP, heat production; Hy, NADPH (in mol); iBW, initial body weight; IE, ingested energy; KFaTs, concentration of FAs needed to reach half the maximal velocity of reaction incorporating FAs into storage TG; Km, concentration of substrate needed to reach half the maximal velocity of a reaction; KNaATP, percentage of basal ATP used for sodium potassium ATPase; La, lactate (in mol); LaCd, lactic acid oxidation rate (in mol/d); LaGl, glucose production from lactate (in mol/d); LaGlADP, ADP production from lactate conversion to glucose (in mol/d); ME, metabolizable energy; mGTP, mitochondrial GTP (in mol); mNADH, mitochondrial NADH (in mol); Ox, oxygen (in mol); OXUp, total mol oxygen used; Pb, body protein (in mol); PbAa, amino acids from muscle protein breakdown (in mol/d); PbAaADP, ADP production from body protein degradation (in mol/d); Pl, other slow-turnover proteins (in mol); PlAa, long turnover protein degradation to amino acids (in mol/d); PlAaADP, ADP production from protein degradation of long turnover proteins (in mol/d); PO, phosphate-to-oxygen ratio; Pv, visceral protein (in mol); PvAa, amino acids from visceral protein breakdown (in mol/d); PvAaADP, ADP production from protein degradation of visceral protein (in mol/d); REE, resting energy expenditure; RQ, respiratory quotient; Respiration, ATP use for respiration (in mol/d); [S], blood concentration of substrate; Ts, storage TG (in mol); TsFa, FAs from breakdown of storage TG (in mol/d); Ur, urea (in mol); VCO_2, volume of carbon dioxide produced; VFaTs, maximal velocity of FA incorporation into storage TG (in mol/d); Vmax, maximal velocity of a reaction; VO_2, volume of oxygen consumed.

Materials and Methods

The model diagram (**Fig. 1**) shows the flow of substrates between pools and serves as the basis for equations 1–8 in **Table 1**. State variables include glucose (Gl), amino acids (Aa), body protein (muscle) (Pb), visceral protein (Pv), other slow-turnover proteins (Pl), FAs, and adipose (storage) TGs. Zero or balance pools, i.e., pools that maintain a zero balance (Fig. 1, dashed lines), are acetyl CoA (Ac), lactate (La), and glycerol (Gy). Dashed arrows in Figure 1 are flows of substrates between pools that maintain carbon balance between pools. Mitochondrial and cytoplasmic Ac pools are considered 1 pool. Urea synthesis represents deamination of Aa (urine), which then supply carbon chains for Gl and/or Ac. Fecal excretion is estimated based on the digestibility of Gl, Aa, and TGs, and therefore is not explicitly shown in Figure 1.

The model simulates changes in energy metabolism, body composition, and BW over time with an iteration interval of 1 d (Table 1, equations 9–17). Energy metabolism includes estimating production and use of cytoplasmic and mitochondrial NADH (cNADH and mNADH, respectively), ATP, mitochondrial GTP (mGTP), FADH (equations 9, 10, and 12), oxygen (Ox) (eq. 13), carbon dioxide (Cd) (eq. 16), PO (eq. 14), and heat production (HP) (eq. 11) based on flow of substrates through

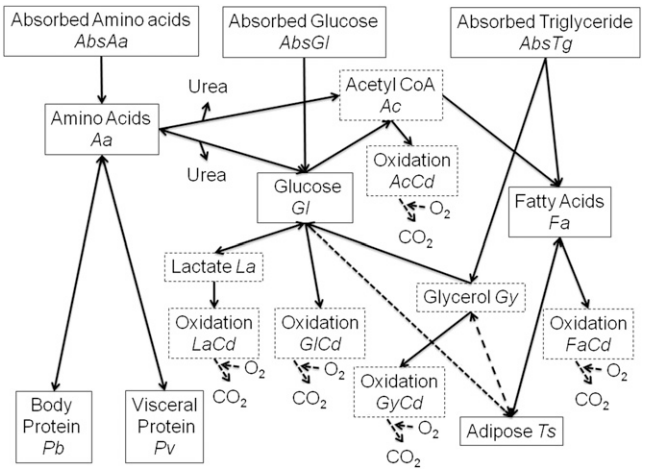

FIGURE 1 Diagram of state variables and their abbreviations in the model of human metabolism. For definitions of abbreviations please see the footnote at the beginning of the article.

TABLE 1 Equations in the human model for lean and obese men[1]

Nonzero substrate pools	Equations	Equation no.
Gl (mol/d)	AbsGl + AaGl + LaGl + GyGl + dGc − GlAa − GlHy − GlAg − GlLa − GlAc − GlCd	1
Ac (mol/d)	GlAc + AaAc + G3PAc + F6PAc − AcHy − AcFa − AcCd	2
Aa (mol/d)	AbsAa + PbAa + GlAa + PvAa + PlAa − AaGl − AaAc − AaPb − AaPv − AaPl − AaCd	3
Pb (mol/d)	AaPb − PbAa	4
Pv (mol/d)	AaPv − PvAa	5
Pl (mol/d)	AaPl − PlAa	6
FAs (mol/d)	AbsTg + AcFa + TsFa − FaTs − FaCd	7
Ts (mol/d)	FaTs − TsFa	8
Energy metabolism		
ADPATP (mol/d)	GlAc × GlAcATP + GlLa × GlLaATP + GlCd × GlCdATP + FaCd × FaCdATP + AaCd × AaCdATP	9
ATPADP (mol/d)	Heart × OxUp + Respiration × OxUp + KNaATP × BasalP + AaPb × AaPbADP + PbAa × PbAaADP + FaTs × FaTsADP + AbsGl × AbsGlADP + AbsAa × AbsAaADP + AbsTg × AbsTgADP + AaPl × AaPlADP + PlAa × PlAaADP + AaPv × AaPvADP + PvAa × PvAaADP + GlHy × GlHyADP + AcHy × AcHyADP + G3Pac × G3PAcADP + F6Pac × F6PAcADP + GlAg × GlAgADP + GyGl × GyGlADP + LaGl × LaGlADP + AcFa × AcFaADP + AaUr × AaUrADP	10
HP (MJ/d)	ATPADP × AtAdHt	11
P (mol/d)	GlCd x GlCdATP + FaCd × FaCdATP + GyCd × GyCdATP + GlAc × GlAcATP + AaCd × AaCdATP	12
Ox (mol/d)	2 × (GlCd × GlCdOx + FaCd × FaCdOx + GlAc × GlAcOx + GyCd × GyCdOX + AaCd × AaCdOx)	13
PO	P / Ox	14
Cd (mol/d)	GlCd × GlCdCd + FaCd × FaCdCd + GyCd × GyCdCd + GlHy × GlHyCd	15
RQ	Cd / Ox	16
ME (MJ/d)	FdIE − (durea × HcUr) − FeNRG	17
EB ME (MJ/d)	ME − HP	18
EBB (MJ/d)	(dPb + dPv + dPl) × HcPb + dTs × HcTg	19

[1] For definitions of abbreviations please see the footnote at the beginning of the article.

metabolic pathways. Estimates of ATP generation and use through each metabolic pathway are based on data from van Milgen (*5*). Yield of ATP from each energy term is a variable so that changes in mitochondrial efficiency can be simulated. Body composition is estimated by Pv and Pb accumulation limited by maximum amounts of DNA accumulation. Therefore, organs and muscle can grow or shrink according to nutrient supply or exercise within an upper limit. Adipose or storage TG (Ts) accumulation is unlimited but dependent on nutrient supply. Changes in BW are the sum of changes in Pb, Pv, and Ts. Other protein turnover rates such as bone and connective tissue (Pl) are assumed to not change. Model predictions include final BW and composition, PO, RQ, energy balance (EB), HP, ME, mols of FAs, Aa, and Gl oxidized (FaCd, AaCd, and GlCd, respectively), and estimates of body and visceral protein and TG turnover (AaPb, PbAa, AaPv, PvAa, FaTs, TsFa, respectively).

Differential equations represent the flow of substrates into and out of whole body nutrient pools (Table 1). Each term in equations 1–8 represents flows of substrates between pools (mol/d), which are dependent on blood Gl (cGl), TG (cTg), Aa (cAa), or FA (cFa) concentrations. Equations for each term are 1 of 2 different forms: Michaelis-Menton–type equations or balance equations, which ensure that zero pools (dashed lines in Fig. 1) do not retain any substrate. Zero pools are Ac, La, and Gy, which correspond to balance equations for production of NADPH from Ac (AcHy), Gl production from lactate (LaGl), and glycerol oxidation rate (GyCd). Michaelis-Menton–type equations are similar in form to those described by Baldwin (*6*). The general form of the equation is as follows.

$$\text{Rate(mol/d)} = \text{Vmax(mol/d)}/(1 + \text{Km}/[\text{S}])$$

Vmax is the maximal velocity of the reaction (mol/d), Km is the concentration of substrate at half maximal velocity (mol/L), and [S] is the current concentration of substrate (mol/L). For example, to represent the synthesis of TG from FAs (FaTs) the equation is FaTs = VFaTs / (1 + KFaTs / cFa). The term VFaTs is the maximal velocity (mol/d) of TG synthesis, KFaTs is the concentration of FAs at half maximal velocity (mol/L), and cFa is the blood concentration of FAs (mol/L). For the Michaelis-Menton–type equation terms Ac from Gl (GlAc), Gl to La (GlLa), adipose synthesis from FAs (FaTs), adipose degradation to FAs (TsFa), and FA oxidation (FaCd), Km is the reference blood concentration cGl 0.007 mol/L, cFa 0.0002 mol/L lean or 0.0004 mol/L obese, cTg 0.0006 mol/L lean or 0.001 mol/L obese, cAc 0.002 mol/L, and cAa 0.003 mol/L from Marques-Lopes et al. (*1*). Vmax was then set to make the terms equal to fluxes in **Table 2**. Other terms associated with fat synthesis and degradation such as NADPH production from Gl through glyceraldehyde 3 phosphate and fructose 6 phosphate (GlHy from G3PAc and F6PAc), the need for NADPH from the malic enzyme (AcHy), FAs synthesized from Ac (AcFa), and glycerol degradation and synthesis (GyGl, GlAg) are based on stoichiometric relations with Fa synthesis (driven by GlAc). Palmitic acid is assumed to be the FA synthesized. Gl is oxidized (GlCd) based on the need for ATP not met by FaCd.

AaCd is 0.415 mol/d for lean and 0.605 mol/d for obese men based on Marques-Lopes et al. (*1*). Aa consumed in excess of oxidation and protein turnover (8) are deaminated to form urea (Ur) for gluconeogenesis (AaGl) or ketogenesis (AaAc). The proportion of gluconeogenic Aa and ketogenic Aa is based on a generalized amino acid profile of animal protein. Protein turnover is classified into 3 different pools based on fast, medium, and slow rates. Rates were set according to Kleiber (*8*). Absorption of nutrients (AbsGl, AbsAa, and AbsTg) is based on diet composition and percent digestibility (*9*).

The model was initially parameterized for a lean 63.5-kg adult man and an obese 96.1-kg adult man who are weight stable and not exercising (*1*). That is, body protein and storage TG pools are not changing in size over time. Initial simulation results based on data from Marques-Lopes et al. (*1*) are compared for the default lean and obese humans in Table 2. Columns 1 and 3 represent observed values from Marques-Lopes et al. (*1*), and columns 2 and 4 represent model simulation results of those values. The sensitivity analyses results are presented in **Table 3**. Then the model was used to simulate experiments from previously published data to examine model responses from lean and obese men for predictions of ingested energy (FdIE) and ME intake (**Table 4**), REE (**Table 5**), and changes in energy metabolism with different diets and body compositions (**Table 6**). For Tables 4–6, data from published studies (first data columns, published values) are compared with model simulation results

TABLE 2 Reference values and model simulation results at the end of a 30-d simulation for the default state of a lean 63.5-kg and an obese 96.1-kg BW and composition-stable sedentary men[1]

Pool sizes and rates	Reference values for lean men	Model values for lean men	Reference values for obese men	Model values for obese men
PO	3 maximum	2.32	3 maximum	2.32
Nonprotein RQ	0.95[2]	0.92	1.05[2]	0.94
EBB, *MJ/d*	0	0	0	0
EB ME, *MJ/d*	0	0	0	0
HP, *MJ/d*	7.1[2]	7.1	8.9[2]	9.2
ME, *MJ/d*	7.1[2]	7.1	8.9[2]	9.2
AbsAa, *mol/d*	0.55[2]	0.55	0.68[2]	0.68
AbsGl, *mol/d*	1.3[2]	1.3	1.6[2]	1.6
AbsTg, *mol/d*	0.070[2]	0.070	0.086[2]	0.086
Pb, *mol*	177[2]	177	267[2]	267
Pv, *mol*	31[2]	31	47[2]	47
Pl, *mol*	259[3]	259	294[3]	294
Ts, *mol*	12.1[2]	12.1	32.4[2]	32.4
cGl, *mol/L*	0.007[2]	0.007	0.007[2]	0.007
cFa, *mol/L*	0.0002[2]	0.0002	0.0004[2]	0.0004
FaCd, *mol/d*	0.285[2]	0.286	0.273[2]	0.274
GlCd, *mol/d*	0.686[2]	0.688	1.05[2]	1.05
AaCd, *mol/d*	0.415[2]	0.415	0.605[2]	0.605
Metabolic processes				
AaPb, PbAa, *mol/d*	1.77[4]	1.77	2.0[4]	2.0
AaPv, PvAa, *mol/d*	2.57[4]	2.56	3.85[4]	3.85
AaPl, PlAa, *mol/d*	0[3]	0	0[3]	0
FaTs, TsFa, *mol/d*	0.29[2]	0.33	0.79[2]	0.80

[1] For definitions of abbreviations please see the footnote at the beginning of the article.
[2] From lean, postprandial men (1).
[3] Calculated based on body composition for slow-protein turnover tissues (7).
[4] Calculated based on ATP use for protein synthesis and TG turnover in lean and obese men from Kleiber (8).

(second data columns, model predictions) with references for the data given in the first column of the tables. Finally, the model was used to predict the impact of changes in protein synthesis based on published rates of energy metabolism (**Table 7**) and changes in mitochondrial efficiency of metabolic flexibility (**Table 8**). Metabolic flexibility is the ability of mitochondria to switch between fuels and is measured by the change in RQ. Therefore, higher changes in RQ between high-fat and high-Gl diets indicate higher metabolic flexibility (21). Results in Table 8 are model simulations in which ATP yield per NADH was altered to represent changes in mitochondrial efficiency and its impact on fuel use (metabolic flexibility) and energy expenditure. Table 7 results are based on changing the reference protein synthesis rates presented in Table 2 to rates from the published studies in Table 7 (column 1, from references listed in the same column).

Data needed to parameterize and simulate energy states include initial BW (iBW) and body composition, diet composition as the percentage of Gl, protein, and TGs (AbsGl, AbsAa, and AbsTg, respectively), and amount eaten. Unfortunately, it was difficult to find published data that included all of the data needed. In those cases, reference values from Table 2 simulations were used. For instance, in Table 4, digestibility data from Kruskall et al. (10) was missing, therefore, default digestibilities were used. In Table 5, references 13 and 14 did not include diet composition, so default diets from Marques-Lopes et al. (1) were used. In Table 6, none of the references included dry matter intake, therefore, default dry matter intakes from Marques-Lopes et al. (1) were used. In Tables 7 and 8, lean and obese models from Table 2 were used and only protein synthesis rates (Table 7, column 1) or ATP yield/NADH were changed (Table 8, column 1).

Model algorithm and software. The model was written in Advanced Continuous Simulation Language (v. 3.0.1.6; Aegis Technologies Group) using a 4th order Runge-Kutta algorithm to perform simulations by numerically estimate differential equation solutions. Global sensitivity analyses (22,23) were then performed to identify what energy parameters (REE, RQ, ME, PO) would be affected the most by changes in input parameters such as BW, energy intake, and oxidation rates (Table 3). Global sensitivity analyses essentially measure the variance attributed to an input relative to the total variance using the Fourier amplitude sensitivity test described by Saltelli et al. (22,23).

Results and Discussion

Other models describing relations between energy intake, energy expenditure, and EB have been published (24–26). These models are based on observational data used to represent cause and effect, i.e., a population approach. The model described herein uses a fundamentally different approach in that tissue substrate use predicts theoretical estimates of ATP creation and use based on metabolic terms representing pathways (an integrative approach). Results from theoretical estimates are then compared with observed data. Both approaches are necessary because models built with observational data will yield better predictions, but models based on an integrative approach will give insight into how tissue metabolic function changes with obesity where understanding and data are lacking.

Mostly mechanistic models of energy metabolism represent theoretical estimates of ATP use and Ox, Cd, and dietary substrate usage. Although theoretical estimates of energy metabolism from models will never exactly predict experimental results because of error, the models will show weaknesses in our understanding of energy transactions and can lead to identifying

TABLE 3 Sensitivity coefficients of key model parameters for predicting REE, RQ, ME, and PO for lean and obese men[1]

	GlCd	FaCd	AaCd	GyCd	LaCd	GlHy	GlAc	FeNRG	AbsTg	FdIE	AaUr	iBW
Lean												
REE	0.43	0.60	0.006	—	—	0.006	—	—	—	—	0.006	0.006
RQ	0.15	0.80	—	0.022	0.022	0.035	—	—	—	—	—	0.022
ME	—	—	—	—	—	—	—	0.013	0	0.98	0	—
PO	0.038	0.32	0.55	0.011	0.011	—	0.011	—	—	—	—	0.011
Obese												
REE	0.43	0.60	0.006	—	—	0.006	—	—	—	—	0.006	0.006
RQ	0.13	0.80	—	0.022	0.022	0.040	—	—	—	—	—	0.022
ME	—	—	—	—	—	—	—	0.014	0	0.98	0	—
PO	0.028	0.24	0.65	0.011	0.011	—	0.011	—	—	—	—	0.011

[1] For definitions of abbreviations please see the footnote at the beginning of the article.

TABLE 4 Results of testing model predictions with previously published data (prediction of ME)[1]

References and parameters	Published values	Model predictions
	MJ/d	*MJ/d*
10[2] (Men, 66–70 y)		
IE	13	13
Energy in urine	0.32	0.32
Energy in feces	2.8	2.8
ME	10	10
REE	6.6	6.6
9[3] (Women)		
Model 1		
IE	9.4	9.4
Energy in urine	0.55	0.81
Energy in feces	0.62	0.47
ME	8.2	8.2
Model 2		
IE	8.1	8.1
Energy in urine	0.47	0.65
Energy in feces	0.29	0.21
ME	7.4	7.3
Model 3		
IE	10	10
Energy in urine	0.27	0.43
Energy in feces	0.39	0.27
ME	9.3	9.3
Model 4		
IE	8.7	8.7
Energy in urine	0.25	0.35
Energy in feces	0.68	0.52
ME	7.8	7.8

[1] For definitions of abbreviations please see the footnote at the beginning of the article.
[2] Model inputs were height, weight, body fat percentage, and carbohydrate, fat, and protein intakes (g/d). REE in model simulations was estimated using the Weir equation (11).
[3] Each model represents a different dietary treatment with different intake energy levels. Model inputs were height, weight, carbohydrate, fat, and protein intakes (g/d), and fecal digestibilities (%).

relations among participant characteristics and their metabolic function. One limitation to this approach is that studies that describe participants, dietary conditions, and metabolic fluxes are difficult to conduct, and therefore, it is hard to find complete data sets in published literature. For this modeling analysis, the lean man model was created first using equations described in Table 1, and then minimal changes were made to parameters within the model to calibrate it for an obese human (Table 2). Specifically, only BW and composition, diet, cFa, AaPb, PbAa, AaPv, PvAa, FaTs, and TsFa, and maximal FaCd were changed to simulate the obese man. Changes made to create the obese man model, however, were all based on data from Marques-Lopes et al. (1). The model was able to duplicate both the lean and obese participants with the exception of the RQ for the obese man (Table 2). Therefore, the models were able to duplicate data from Marques-Lopes et al. (1) for both lean and obese men. Metabolic differences between lean and obese men were higher HP, ME, body protein, body fat, blood TGs, GlCd, AaCd, and rates of protein and fat turnover in obese men. FaCd, however, was lower in obese men. As described in Marques-Lopes et al. (1), much of these changes are expected in obese men because of higher intakes, increased BW, and increased organ sizes for processing nutrients from higher daily intakes.

RQ estimates for obese participants (1) varied from 0.82 to 1.1 and from 0.81 to 0.95 for lean participants over a 6-h period that included a test meal. There is considerable error in measurement of RQ depending on timing of the diet and the length of measurement. Therefore, under prediction of RQ in the obese model is still within range of observed values. Interpretation of RQ usually only considers GlCd and FaCd. With model predictions, if only GlCd and FaCd are considered, RQ predictions are as expected; RQ = 1 for complete Gl oxidation and RQ = 0.7 for complete FA oxidation. However, the model also includes oxidation of La, Gy, and Ac in addition to FaCd and GlCd. Supply of Gy and Ac for oxidation are dependent on TG turnover. Although predictions of RQ by the model are mostly sensitive to GlCd and FaCd, Gy and La affect RQ and FA synthesis (AcFa—NADPH production from Gl). Experimental estimates of these oxidation rates with estimates of RQ would improve predictions, and it is possible that there are other substrate oxidation rates that are not included in the model that may provide better predictions of RQ.

The model was able to predict ME well based on FdIE (Table 4). However, partitioning of energy excretion as urea was overpredicted and feces were underpredicted with data from Coles et al. (9). For all diets, FdIE had to be increased in the model to match published values, indicating that dietary means and energy measurements were insufficient to represent energy intake. The model is very sensitive to nutrient

TABLE 5 Results of testing model predictions with previously published data (prediction of REE)[1]

References and parameters	Published values	Model predictions
	MJ/d	*MJ/d*
12 (Men and women, BMI $<$ 18.5 kg/m^2)		
ME	8.4	8.4
REE[2]	4.1	5.4
12 (Men and women, BMI 19–28 kg/m^2)		
ME	10	10
REE[2]	6.6	6.6
12 (Men and women, BMI $>$ 30 kg/m^2)		
ME	9.9	9.9
REE[2]	7.1	7.2
13 (Men, 22–31 y, BMI 22.5 kg/m^2)		
REE[3]	7.2	7.2
13 (Men, 60–82 y, BMI 25 kg/m^2)		
REE[3]	5.7	6.4
14 (Women, 34–40 y, BMI 20 kg/m^2)		
REE[3]	5.6	6.0
14 (Men, 23–40 y, BMI 24 kg/m^2)		
REE[3]	8.0	7.5
15 (Men, 18–28 y, intake 3250 kcal/d)		
ME	13	13
REE[2]	7.9	8.1
15 (Men, 18–28 y, intake 1950 kcal/d)		
ME	8.2	8.2
REE[2]	7.0	8.0

[1] For definitions of abbreviations please see the footnote at the beginning of the article.
[2] Model inputs were height, weight, body fat percentage, body protein, visceral mass, and carbohydrate, fat, and protein intakes (g/d). REE was estimated using the Weir equation (11).
[3] Model inputs were BW and composition data.

TABLE 6 Results of model predictions of energy metabolism with previously published diets and participant descriptions[1]

References and diets	Diet descriptions	Published values		Model predictions			
		RQ	REE	GlCd	FaCd	RQ	REE[2]
	% Energy intake		*MJ/d*	*mol/d*	*mol/d*		*MJ/d*
16 (Men and women)[3]							
CHO	57	0.83	7.8	0.13	0.522	0.83	7.8
Fat	27						
Protein	15						
16 (Men and women)[4]							
CHO	45	0.82	7.8	0.10	0.522	0.82	7.8
Fat	27						
Protein	27						
17 (Men)[5]							
CHO	50	0.85	—	0.047	0.478	0.86	8.3
Fat	35						
Protein	15						
18 (Men and women)[6]							
CHO	60	0.86	8.3	0.30	0.48	0.87	8.3
Fat	20						
Protein	20						
18 (Men and women)[7]							
CHO	20	0.75	8.0	0.035	0.522	0.80	8.0
Fat	60						
Protein	20						
18 (Men and women)[8]							
CHO	35	0.79	8.6	0.017	0.539	0.81	8.6
Fat	45						
Protein	20						

[1] For definitions of abbreviations please see the footnote at the beginning of the article.
[2] REE was estimated using the Weir equation (13).
[3] Model inputs were BW = 93.7 kg, body fat = 40.4 kg, FFM = 50.5 kg, ME = 8.2 MJ/d.
[4] Model inputs were BW = 93.7 kg, body fat = 40.4 kg, FFM = 50.5 kg, ME = 8.1 MJ/d.
[5] Model inputs were BW = 69 kg, body fat = 12.3 kg, FFM = 60.8 kg, ME = 12 MJ/d.
[6] Model inputs were BW = 96.9 kg, body fat = 33 kg, FFM = 63.6 kg, ME = 9.8 MJ/d.
[7] Model inputs were BW = 96.9 kg, body fat = 33 kg, FFM = 63.6 kg, ME = 9.6 MJ/d.
[8] Model inputs were BW = 96.9 kg, body fat = 33 kg, FFM = 63.6 kg, ME = 11 MJ/d.

intake (g/d) as indicated by a very large sensitivity value for FdIE in Table 3. In most cases, rounding up mean IE intake values for protein, fat, and carbohydrates resulted in matching published IE intakes. Data from Coles et al. (9) included apparent fecal digestibilities, which were used in the model to predict fecal energy excretion but did not improve predictions

TABLE 7 Results of model predictions of energy metabolism with previously published rates of fractional protein synthesis[1]

References and tissues	Published protein FSR[2]	Lean model predictions				Obese model predictions			
		GlCd	FaCd	RQ	REE	GlCd	FaCd	RQ	REE
	%/d	*mol/d*	*mol/d*		*MJ/d*	*mol/d*	*mol/d*		*MJ/d*
8									
Viscera	8.5	0.69	0.29	0.92	6.4	1.2	0.27	0.92	8.2
Muscle	0.99								
19[2]									
Splanchnic	12	0.90	0.29	0.89	7.0	1.5	0.27	0.95	9.1
Muscle	1.5								
20									
Muscle	0.72	0.59	0.29	0.88	6.0	1.2	0.27	0.94	8.0
20									
Muscle	2.1	0.88	0.29	0.92	6.9	1.5	0.27	0.95	9.0

[1] For definitions of abbreviations please see the footnote at the beginning of the article.
[2] Participant descriptions were not included in the article; therefore, the lean and obese men defaults including diets (Table 2) were used.

TABLE 8 Results of model predictions of metabolic flexibility[1]

	FaCd	GlCd	RQ	REE
	mol/d	*mol/d*		*MJ/d*
Lean				
ATP yield/NADH = 2.25	0.29	0.69	0.88	6.4
ATP yield/NADH = 1	0.29	1.9	0.95	9.8
Obese				
ATP yield/NADH = 2.25	0.27	1.2	0.94	8.1
ATP yield/NADH = 1	0.27	2.8	0.96	13

[1] For definitions of abbreviations please see the footnote at the beginning of the article.

of energy excretion partitioning in feces. In addition, the model does not represent endogenous energy losses, which could account for some of the discrepancies among published values and model predictions. However, fecal energy has a relatively low contribution to estimates of ME (Tables 3 and 4), and therefore, estimates of ME by the model are very close to experimental values.

Prediction of REE was more problematic than prediction of ME intake (Table 5). REE is predicted in the model based on the Weir equation (11). The abbreviated Weir equation uses volume of carbon dioxide produced (VCO_2) and volume of oxygen consumed (VO_2) to predict REE, and so model predictions are based largely on oxidative metabolism. The model is also more sensitive to GlCd and FaCd than diet and BW when predicting REE (Table 3). However, REE was consistently overpredicted in underweight, older, and women participants as well as participants who lacked body composition data and ME intake as inputs to the model. This agrees with results from Westphal et al. and Gallagher et al. (12–14), which found that fat-free mass accounted for a majority of the variation in REE and that skeletal mass and liver mass accounted for 86% and 48% of the variation in REE, respectively. When calorie intakes were matched in the model but groups differed in BW and composition (12–14), predictions of REE changed to match observed results (data not shown). Because the Weir equation does not include body composition data in its predictions, the ability of the model to predict REE at lower REE values was limited. However, body composition data within the model could be manipulated to match REE values for all participants. These simulation results suggest that it is important to measure and report body composition and ME to estimate REE in addition to VCO_2 and VO_2. Table 6 shows an improvement in model results when more detailed information on body composition and energy intake are included in participant and treatment descriptions.

The model did predict the effect of changing diets on fuel use (GlCd, FaCd, RQ, and REE) (Table 6). Viscera and connective tissue mass and dry matter intakes were adjusted to match published values of ME and REE. FaCd was the primary determinant of RQ (Table 3) and was lower for moderately obese and obese simulations leading to higher predictions of GlCd. A lowered ability to use FAs as fuel in obese participants was observed (1,21,27) and is also supported by model simulation results.

Predictions of RQ are dependent on maximal velocity of fat oxidation, which appears to be closely related to the relative fatness of the participant. Therefore, model results suggest that the level of obesity may be a predictor of RQ. Protein turnover rate also changes REE and RQ (Table 7). Previous estimates of actively metabolic tissue and muscle fractional protein synthesis rates range from 8.5% to 12%/d and 0.72% to 2.06%/d, respectively. Using these rates to set protein turnover rates increased RQ with muscle protein and viscera turnover in the lean model but only viscera protein turnover in the obese model. REE predictions increased 0.60–1.0 MJ/d with higher increases in the obese model predictions because of larger estimates of visceral mass. Similarly, decreasing ATP yield (decrease mitochondrial efficiency) increased GlCd in both models, but increases in REE and RQ were small in the obese model compared with lean model predictions. In the lean model simulations, the higher energy demand of increased protein turnover increases REE and results in more GlCd. But, in the obese model simulations, the small increase in REE and RQ is due to already higher energy costs associated with more visceral and splanchnic tissue and requiring more GlCd and amino acid oxidation (Table 3) to supply energy for increased protein turnover.

Simulations using the lean and obese models to show changes in metabolic flexibility caused by decreased mitochondrial efficiency show similar results (Table 8). Decreased mitochondrial efficiency in the lean human increases REE and RQ because more Gl must be oxidized to maintain EB. Metabolic flexibility or the change in RQ is 0.07 for the lean simulations compared with 0.02 for the obese simulations. GlCd and REE also increase for the obese human, but metabolic flexibility is much lower, implying an inability of obese participants to burn fuels other than Gl.

Mathematical models representing theoretical estimates of metabolism and energy creation and use can be useful tools to help explain and predict relations among metabolic parameters that account for differences in energy use among individual participants. Because fat mass is directly related to REE predictions and FaCd, Ts could be used as a predictor of RQ. The model is also able to predict increased energy requirements caused by increased tissue turnover rates and metabolic flexibility caused by increasing energy requirements.

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H.A.R. designed and conducted the research, analyzed the data, and wrote the paper; and C.C.C. provided essential constructs for building the model. Both authors read and approved the final manuscript.

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