Chapter 22
Quantitative Physiology of Human Starvation: Adaptations of Energy Expenditure, Macronutrient Metabolism and Body Composition

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22.1 Introduction

On October 19, 2003, magician David Blaine emerged from a clear plastic box that had been suspended 40 feet over the River Thames in London after 44 days of self-imposed starvation. His weight had been trimmed by 24.5 kg and his blood and urine showed the tell-tale signs of prolonged starvation (Jackson et al. 2006; Korbonits et al. 2005, 2007), despite the skepticism of much of his worldwide audience. In a world where one of the most pressing health issues is the rise of a global obesity epidemic (Swinburn et al. 2011), it is understandable how such prolonged fasting would be met with disbelief by a mostly well-fed western world.

Mr. Blaine's fast was a recent addition to a long history of 'hunger artists' who starved professionally for entertainment. This phenomenon reached its peak of popularity in the late nineteenth and early twentieth centuries and was popularized in the 1922 short story *A Hunger Artist* by Franz Kafka (see also Lignot and LeMaho, Chap. 2). Prolonged starvation has also been used as a form of protest by 'hunger strikers' who have occasionally died as a result (Leiter and Marliss 1982) (see also Grant, Chap. 21). Of course, famine is the most common historical cause of human starvation which continues to the present day despite the fact that the world wastes an enormous amount of food (Hall et al. 2009; Stuart 2009).

Prolonged periods of food scarcity were likely frequent occurrences over the course of human evolution (Prentice 2005) and have resulted in complex physiological adaptations that allow humans to survive for extended periods between feeding opportunities (Chakravarthy and Booth 2004). Modern scientific investigation of human starvation began in the late nineteenth and early twentieth

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centuries with the most comprehensive being Francis Gano Benedict's 1912 study of Agostino Levanzin's 31-day fast in Boston (Benedict 1915). In this chapter, I will simulate Benedict's classic starvation experiment using a recently developed computational model of human metabolism (Hall 2006, 2010). In particular, I will use the model simulations along with Benedict's data to illustrate the coordinated metabolic response to starvation with a focus on the dynamic changes of energy expenditure, metabolic fuel utilization, body weight, and body composition. This chapter will also illustrate how the greatly expanded energy stores of obese people can allow them to survive for remarkably long periods of starvation.

22.2 Computational Model of Human Metabolism

Maintaining life and performing physical work requires energy and the body derives its energy from the controlled combustion of three macronutrients: carbohydrate, fat, and protein. These macronutrients are obtained from the diet with about 50% of the energy derived from carbohydrate, 35% from fat, and 15% from protein (Austin et al. 2011). However, these average diet proportions can vary widely from person to person and also from day to day. Complex physiological mechanisms maintain normal functioning of the body despite marked fluctuations of diet quantity and composition. These mechanisms are required to operate both in periods of food surplus as well as scarcity.

While the molecular, cellular, and physiological mechanisms underlying the regulation of human metabolism and body weight are exceedingly complex, the whole-body system obeys thermodynamic laws that constrain its dynamics in ways that make the overall system amenable to mathematical modeling (Chow and Hall 2008). For example, the first law of thermodynamics requires that energy is conserved and therefore changes in the body's energy content must be associated with an imbalance between the rate of food energy intake and the rate of energy expenditure. Similarly, macronutrient imbalances between dietary intake and metabolic utilization underlie changes in stored fat, glycogen, and protein and result in changes in the body composition.

I recently developed a mechanistic computational model of human macronutrient metabolism and body composition change (Hall 2006, 2010). The model was designed to quantitatively track the metabolism of all three dietary macronutrients and their interactions within the human body. The main model assumptions were that energy must be conserved and that changes in the body composition result from imbalances between the intake and utilization rates of fat, carbohydrate, and protein along with intracellular and extracellular fluid changes. The model was developed using published human data from over 50 experimental studies and was the first to model all three dietary macronutrients and accurately simulate the metabolic responses to various diets in a wide variety of subject groups, including lean and obese men and women.

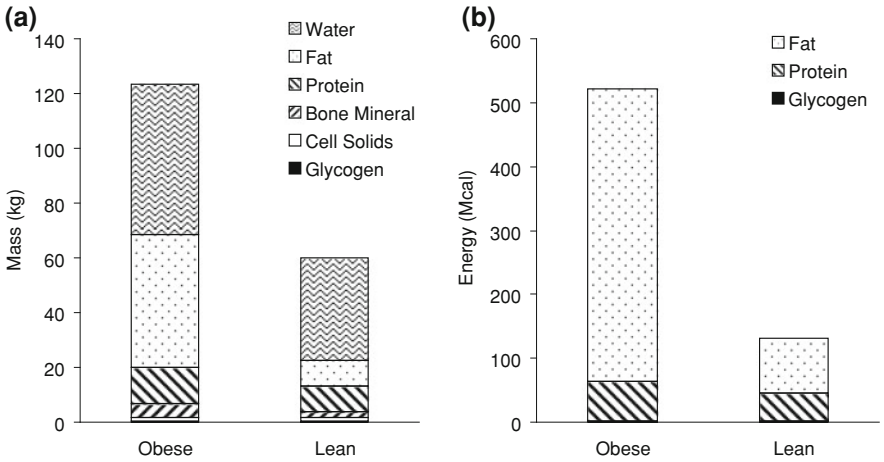

Fig. 22.1 **a** The chemical composition of an obese man (*left*) differs from that of a lean man (*right*) primarily as a result of the increased fat mass. **b** The body energy stores are greatly expanded in the obese man as a result of the increased body fat mass

The computational model predicts how diet changes result in adaptations of whole-body energy expenditure, metabolic fuel selection, and various whole-body metabolic fluxes (e.g., lipolysis, lipogenesis, gluconeogenesis, ketogenesis, protein turnover, etc.) that ultimately give rise to changes in body weight and composition. I previously used the computational model to better understand the metabolic changes that take place during prolonged semi-starvation and re-feeding (Hall 2006), exemplified by the classic Minnesota experiment of Keys (Keys 1950). In this chapter, I present the first simulation of the quantitative changes in macronutrient metabolism and body composition that take place during complete starvation in lean and obese humans.

22.3 Human Body Composition

Figure 22.1a illustrates the chemical composition of an average obese male along with the composition of the lean subject of Benedict's prolonged fasting study. Water is typically the greatest body component of both obese and lean men, but obesity is characterized by a greatly expanded body fat mass that can become the majority body constituent with morbid obesity. The absolute masses of body protein and bone mineral are also increased in obesity, but to a much lesser extent. Glycogen and cellular solids, such as potassium and nucleic acids, contribute a small fraction of the body's overall mass.

Body fat, protein, and glycogen comprise the stored energy of the body and these stores must be mobilized when the diet is insufficient to meet the body's

energy requirements. Figure 22.1b illustrates the composition of the body in terms of its energy content with fat stored in adipose tissue providing the overwhelming majority of the available stored energy, especially in obesity. Despite dietary carbohydrate providing the majority of the body's energy demands on a daily basis, glycogen represents a relatively insignificant store of energy ($\sim$2,000 kcal). Thus, the transition from fed to fasted states must coincide with a substantial shift of metabolic fuel utilization away from carbohydrate oxidation and toward fat oxidation. Otherwise, glycogen could only provide enough fuel to survive for a few days. Body protein represents a substantial amount of energy, but in humans it is not a storage pool in the same sense as adipose tissue triglyceride (compare with Bauchinger and McWilliams, Chap. 12). Rather, body proteins are functionally important and cannot be depleted by a significant fraction without serious complications and death. In contrast, fat stores represent a considerable energy reserve and body fat can be depleted to very low levels without substantial functional impairments (Friedl et al. 1994; Leiter and Marliss 1982).

22.4 Body Weight Loss During Starvation

A continuous supply of energy is required to maintain life and perform physical work. When dietary intake of macronutrients is insufficient to provide for the energy needs of the body, the deficit is taken from the stored energy pools and weight loss ensues as these storage pools decrease in size. Figure 22.2a shows the time course of weight loss during Levanzin's 31-day fast (closed circles) as well as the average weight loss in 18 obese men (open circles) observed by Runcie et al. (Runcie and Hilditch 1974) over the course of a 30-day fast. The computational model simulations of body weight change are shown in the curves and agree reasonably well with the data despite the fact that no model parameters were adjusted and these data were not used in model development (Hall 2006, 2010).

Over the first week of the fast, weight loss was rapid as a result of significant body water decrease. This water loss was the result of decreased glycogen, which binds $\sim$3 grams of water per gram of glycogen, as well as loss of extracellular water to maintain sodium homeostasis in the absence of dietary sodium. Following the rapid water loss, weight was lost linearly over the remaining weeks at similar rates in both the lean and obese subjects. However, the rate of body fat loss was substantially greater in the obese ($\sim$1.4 kg per week) compared to the lean man ($\sim$1 kg per week). The increased rate of fat loss in obesity was the result of the greater energy deficit elicited by the fast since the obese man had a higher energy expenditure rate (Fig. 22.2b) and the greater resulting energy deficit during the fast was met with increased mobilization of energy stores from body fat.

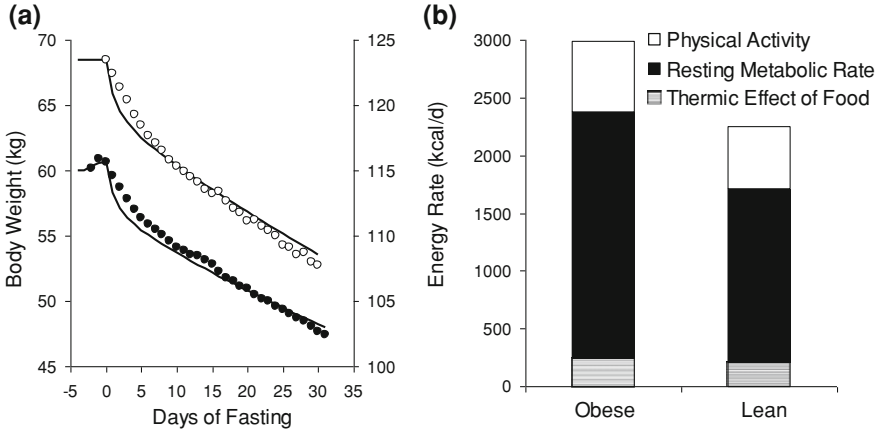

Fig. 22.2 **a** Weight change during starvation in Benedict's lean subject (●, *left axis*) and the average weight of obese subjects during starvation (○, *right axis*). The curves correspond to the computational model simulations. **b** Components of the baseline energy expenditure rate in the average obese man (*left*) and the lean man (*right*)

22.5 Energy Expenditure

22.5.1 Components of Energy Expenditure

Figure 22.2b illustrates three components of human energy expenditure at baseline in relatively sedentary lean and obese men. The obese man required several hundred additional kcal/d to maintain his weight compared to the lean man. Typically, the smallest component of the total energy expenditure rate is the thermic effect of food (sometimes also called 'diet induced thermogenesis' or 'specific dynamic action') defined as the increase of metabolic rate observed for several hours following the ingestion of a meal. The thermic effect of food is believed to represent the energy cost of digestion and absorption as well as the storage and metabolic fate of dietary macronutrients (Westerterp 2004). While the precise mechanisms underlying the thermic effect of food are not understood, there is a clear dietary macronutrient hierarchy in the magnitude of the metabolic rate increase after feeding, with protein causing a greater increment than carbohydrate which is greater than that of fat (reviewed in McCue 2006).

The resting metabolic rate corresponds to the energy expended by the body when not performing physical work and typically is the largest contribution to the total energy expenditure. Contrary to popular belief, obese people generally have higher absolute resting metabolic rate compared to lean people (Fig. 22.2b). The main contributor to the resting metabolic rate is the fat-free mass of the body which is elevated in obesity along with the increased adipose tissue mass which also contributes to their increased resting metabolic rate. The linear relationship

between resting metabolic rate and fat-free mass is identical in obese and lean people (Cunningham 1991; Weyer et al. 1999). This means that the elevated resting metabolic rate in obesity is in line with what is expected for their body composition.

Physical activities typically involve locomotion and the energy costs are determined by the duration and intensity of physical activity in proportion to the overall body weight. Thus, obese and lean people can have similar daily energy costs for physical activity (Fig. 22.2b) despite obese people typically being less active. With weight loss, it costs less energy to perform most physical activities and therefore the energy expended for physical activity typically decreases with starvation unless the quantity or intensity of physical activity increases to compensate.

22.5.2 Measurement of Energy Expenditure by Indirect Calorimetry

Human energy expenditure is typically measured using indirect calorimetry where oxygen consumption, carbon dioxide production, and nitrogen excretion provide quantitative measurements of the macronutrient oxidation rates that supply the body's energy needs (Bursztein et al. 1989). Oxidation of dietary macronutrients yields chemical energy and Hess's law states that the energy released is the same regardless of whether the macronutrients are combusted in a bomb calorimeter or catabolized via the oxidative phosphorylation in the cellular mitochondria. Thus, the energy released from oxidation of macronutrients in the body is identical to that measured using direct calorimetry in the laboratory. However, there is an important caveat. Not all macronutrients in food are completely absorbed by the body. Furthermore, the dietary protein that is absorbed does not undergo complete oxidation in the body, but rather produces urea and ammonia. In accounting for these effects, the 'metabolizable' energy content of carbohydrate, fat, and protein is slightly less than the values obtained by bomb calorimetry (Livesey 1984; Livesey and Elia 1988).

The theoretical basis of indirect calorimetry relates oxidation of carbohydrate, fat, and protein and the heat produced by these processes to the measured oxygen consumption, carbon dioxide production, and nitrogen excretion as follows:

$$1\text{ g Carbohydrate} + 0.831\text{ L } O_2 \rightarrow 0.831\text{ L } CO_2 + 0.6\text{ g } H_2O + 4.2\text{ kcal}$$

$$1\text{ g Fat} + 2.03\text{ L } O_2 \rightarrow 1.43\text{ L } CO_2 + 1.09\text{ g } H_2O + 9.4\text{ kcal}$$

$$1\text{ g Protein} + 0.966\text{ L } O_2 \rightarrow 0.782\text{ L } CO_2 + 0.45\text{ g } H_2O + 0.16\text{ g N} + 4.7\text{ kcal}$$

Therefore, the volumes of oxygen consumed and carbon dioxide produced (VO_2 and VCO_2, respectively) are primarily determined by the amount of

carbohydrate, fat, and protein oxidized. Also, nitrogen excretion, N, is determined by protein oxidation. Therefore, we have the following three equations for the quantities measured via indirect calorimetry in terms of the carbohydrate, fat, and protein oxidized in grams (C, F, and P, respectively):

$$VO_2(L) = 0.831(L/g) \times C(g) + 2.03(L/g) \times F(g) + 0.966(L/g) \times P(g)$$

$$VCO_2(L) = 0.831(L/g) \times C(g) + 1.43(L/g) \times F(g) + 0.782(L/g) \times P(g)$$

$$N(g) = 0.16 \times P(g)$$

These three linear equations for C, F, and P can be solved in terms of the VCO_2, VO_2 and N measurements:

$$C(g) = 4.07(g/L) \times VCO_2(L) - 2.87(g/L) \times VO_2(L) - 2.58 \times N(g)$$

$$F(g) = 1.67(g/L) \times VO_2(L) - 1.67(g/L) \times VCO_2(L) - 1.92 \times N(g)$$

$$P(g) = 6.25 \times N(g)$$

Therefore, the total energy expended, E, is the sum of the energy released during the oxidation of carbohydrate, fat, and protein:

$$E(kcal) = 4.2(kcal/g) \times C(g) + 9.4(kcal/g) \times F(g) + 4.7(kcal/g) \times P(g)$$

$$E(kcal) = 3.745(kcal/L) \times VO_2(L) + 1.285(kcal/L) \times VCO_2(L) + 0.484(kcal/g) \times N(g)$$

While other metabolic processes, such as de novo lipogenesis and gluconeogenesis, also contribute to respiratory gas exchange, their relatively minor contribution is typically ignored for calculation of the total energy expenditure rate.

22.5.3 Dynamics of Energy Expenditure During Starvation

The curves in Fig. 22.3a illustrate the computational model simulations and the open and closed circles represent the measured daily oxygen consumption and carbon dioxide production rates, respectively, during the 31-day fasting experiment of Benedict. Both the model and the data show the characteristic decline of respiratory exchange which translates into a decrease of daily energy expenditure shown as open circles in Fig. 22.3b. By measuring respiratory exchange rates when the subject was at rest, the indirect calorimetry equations provide a measure of resting metabolism. The closed circles in Fig. 22.3b illustrate that the measured resting metabolic rate also slows as the fast progresses in agreement with the computational model simulation.

The mechanism for the slowing of resting metabolism during the fast can only partially be explained by the reduction in body weight and metabolically active

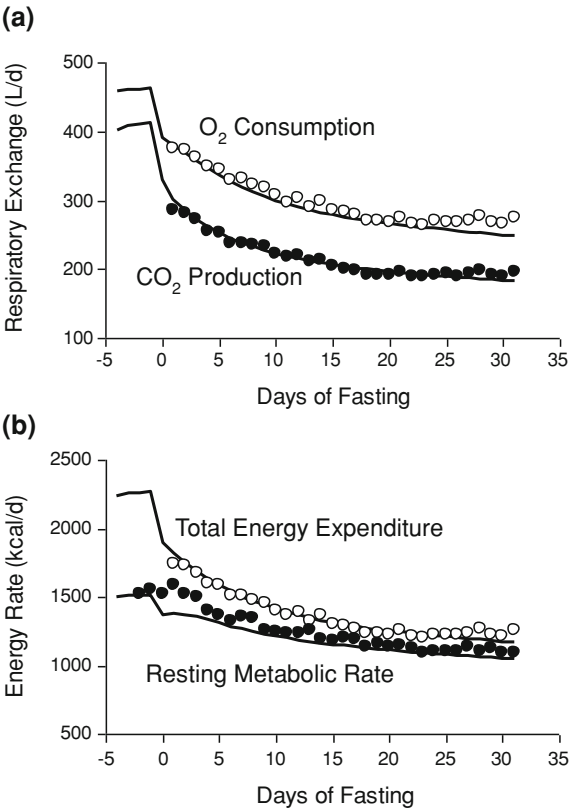

Fig. 22.3 **a** Oxygen (O_2) consumption rate (○) and carbon dioxide (CO_2) production rate (●) measured in Benedict's lean subject during starvation. The curves illustrate the computational model predictions. **b** Measured total energy expenditure rate (○) and resting metabolic rate (●) along with the computational model predictions (*curves*)

lean tissue mass. Decreased flux through energy-requiring metabolic pathways (e.g., de novo lipogenesis and protein synthesis) also contributes to reduced energy expenditure with starvation, but the observed reduction is greater than can be explained based on these changes (see also McCue et al., Chap. 8). Rather, a metabolic adaptation to the dietary energy deficit appears to take place that further slows metabolic rate and this energy savings can amount to several hundred kcal/d (Doucet et al. 2003, 2001; Leibel et al. 1995). The mechanistic basis for such an adaptive decrease of thermogenesis is unknown, but may involve reduced sympathetic tone, thyroid activity, and decreased circulating leptin (Rosenbaum et al. 2000; Weinsier et al. 2000).

It makes evolutionary sense to improve the energy efficiency of the body during periods of food scarcity to optimize the survival time until the next feeding opportunity. Our teleological expectation is that greater energy stored in body fat (Fig. 22.1b) should allow for greater starvation survival time in obesity (see Sect. 22.8) and the requirement for metabolic slowing would not be as critical for survival in the obese. Therefore, we might expect that the magnitude of metabolic slowing would be attenuated by the body fat mass. However, the computational

model predicts that the magnitude of the metabolic slowing is proportional to the decrease of energy intake from baseline (Hall 2006, 2010). Since baseline energy intake is typically greater in obese versus lean people, this means that the model predicts a greater adaptive metabolic slowing during starvation in the obese. While much work remains to properly validate this model prediction, I have previously demonstrated that the model accurately predicts metabolic adaptations to underfeeding in both lean and obese people (Hall 2006, 2010). If the model predictions are correct, this suggests that there has been little evolutionary pressure to attenuate the metabolic slowing based on the body fat mass—much to the dismay of obese dieters.

22.6 Metabolic Fuel Selection and Mobilization

Regulation of metabolic fuel selection plays a prominent role in the physiological adaptation to starvation. For example, while carbohydrate is the majority macronutrient of the western diet, only a few days worth of glycogen is stored in the body which necessitates dramatically decreasing carbohydrate oxidation shortly after the onset of starvation and switching to fat and protein metabolism to provide the metabolic fuels of the body. Thus, a coordinated metabolic response ensues during starvation to increasingly draw energy from fat stores to provide the bulk of the body's energy requirements.

The ratio of carbon dioxide production to oxygen consumption provides an index of metabolic fuel selection since this ratio, called the respiratory quotient (RQ), is equal to 1 for pure carbohydrate oxidation and 0.7 for pure fat oxidation. Thus, the value of the RQ provides an objective estimate of the metabolic fuel mix. Figure 22.4a shows the simulated and measured RQ during the Benedict experiment and indicates the prominence of carbohydrate oxidation prior to the fast and a rapid switch to fat oxidation over the first several days of fasting.

Figure 22.4b illustrates the simulated rates of carbohydrate, fat, and protein oxidation in the Benedict experiment as the fast progresses. These shifting macronutrient oxidation rates over the course of the fast are determined by the altered fuel delivery rates from the carbohydrate, fat, and protein reserves stored in the body tissues. In the first days of starvation, circulating glucose and insulin concentrations decrease, glucagon levels increase, and glycogen is mobilized from the liver and skeletal muscle. As glycogen depletes, glycogenolysis decreases (Fig. 22.5a). The decrease of insulin results in an increase in adipose tissue lipolysis (Fig. 22.5a) thereby resulting in increased mobilization of free fatty acids and glycerol (see also Price and Valencak, Chap. 15). The glycerol is transformed into glucose via gluconeogenesis in the liver and kidneys which also use some amino acids (alanine in particular) as gluconeogenic substrate (Fig. 22.5c). Increased gluconeogenesis ensures that the decrease of circulating glucose is not so severe as to seriously impair brain functioning which primarily relies on glucose as its metabolic fuel in the fed state and in the initial days of starvation.

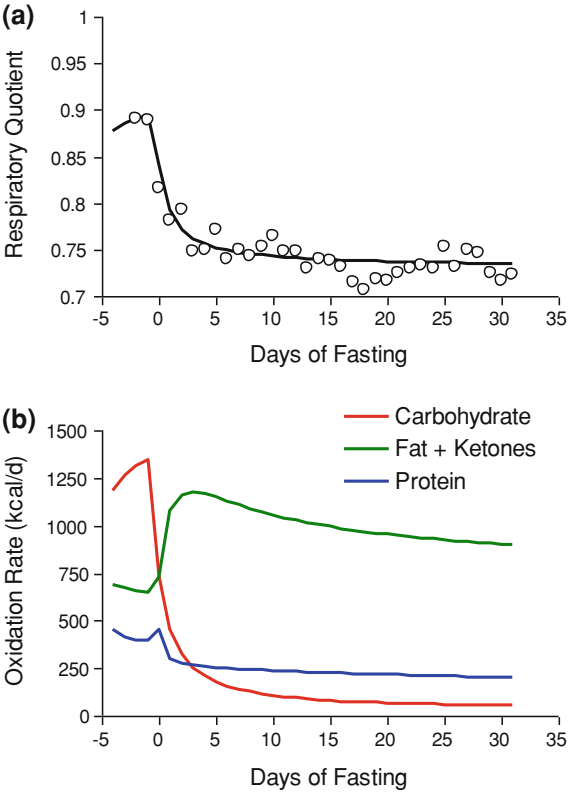

Fig. 22.4 **a** Measured respiratory quotient (○) in Benedict's subject during starvation along with the computational model prediction (*curve*). **b** Computational model predictions of the rates of carbohydrate, fat, ketone, and protein oxidation during starvation

The augmented adipose tissue lipolysis increases free fatty acid supply to the liver which, in the context of low circulating insulin, results in an increase in ketogenesis over the first week of starvation (Fig. 22.5c). Apart from glucose, ketones are the only major fuel source for the brain and the vast majority of the ketones produced by the liver are oxidized. However, as the circulating ketone levels exceed the renal threshold a small fraction are spilled in the urine as shown in the curve in Fig. 22.5d along with the corresponding data from Benedict's subject. These coordinated hormonal and metabolic adaptations to starvation were unknown to Benedict at the time of his fasting experiment. Fifty years later, the classic work of George Cahill and colleagues led the way in elucidating these regulatory mechanisms of human starvation (reviewed in (Cahill 1970, 2006)) that were simulated by the computational model.

22.7 Macronutrient Imbalance and Body Composition Change

During starvation, the macronutrient utilization rates described above define the net macronutrient imbalances depicted in Fig. 22.6a. The fat imbalance contributed the majority of the energy imbalance following the first few days of the fast

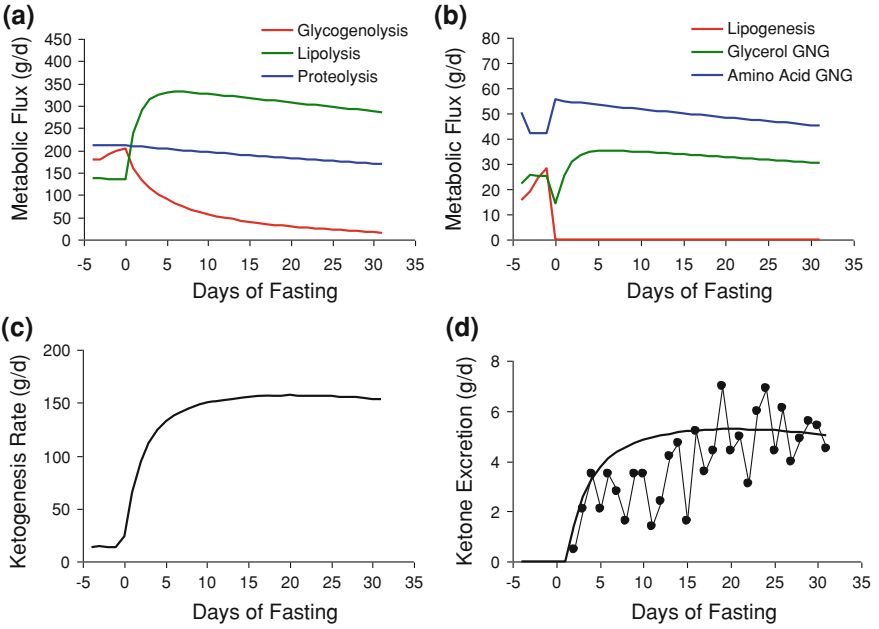

Fig. 22.5 **a** Computational model simulations of whole-body glycogenolysis, lipolysis, and proteolysis during starvation in Benedict's lean subject. **b** Simulated rates of de novo lipogenesis and gluconeogenesis (GNG) from glycerol and amino acids. **c** Simulated ketone production rate during starvation. **d** Measured ketone excretion rate (●) along with the computational model simulation (*curve*)

whereas the carbohydrate imbalance was transient and the protein imbalance was modest but relatively sustained over time. These imbalances were accounted for by decreases of stored glycogen, fat, and protein in the body and Fig. 22.6b illustrates the predicted changes over the course of Levanzin's fast.

About 3 grams of intracellular water are bound to each gram of stored glycogen, and about 1.6 grams of water are bound per gram of protein. These intracellular water changes, along with the extracellular fluid shifts corresponding to maintenance of sodium homeostasis, resulted in the model predicted the fat-free mass changes shown in Fig. 22.6c. Interestingly, while most of the energy imbalance was accounted for by fat, and fat loss was quantitatively larger than the losses of body protein or glycogen, more fat-free mass was lost than fat mass as a result of body water changes. The vast majority of the extracellular water loss occurred within the first several days of the fast and was the major contributor to the early loss of fat-free mass and rapid initial weight change. Thereafter, both fat mass and fat-free mass decreased approximately linearly.

Figure 22.6d illustrates the predicted average fat mass and fat-free mass changes in the fasting obese men investigated by Runcie. Similar to the Benedict data, fat-free mass had a rapid initial reduction due to extracellular fluid loss followed by a linear phase of parallel loss fat-free mass and fat mass. About 1.8 kg more fat mass

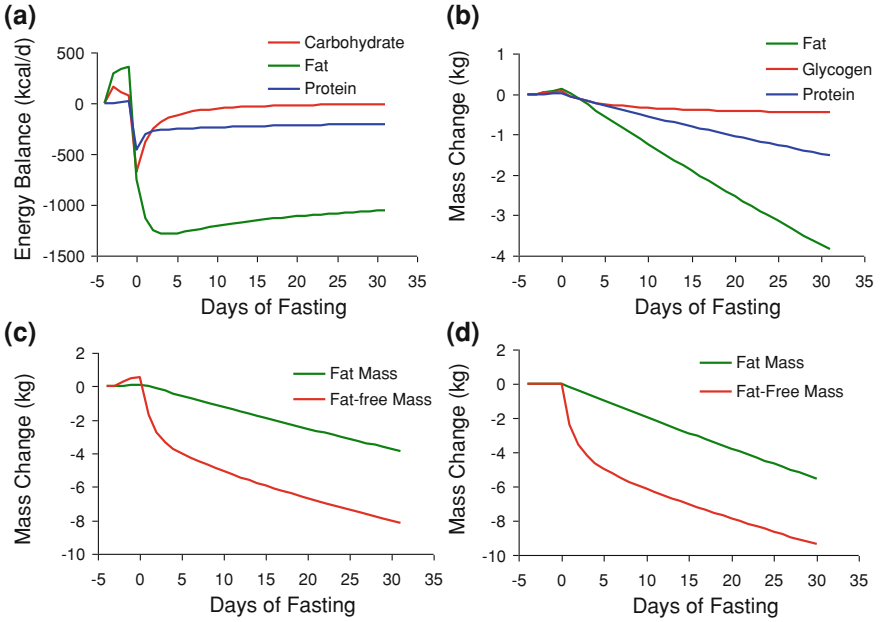

Fig. 22.6 **a** Daily net macronutrient imbalances simulated by the computational model in Benedict's starving lean subject. **b** Simulated changes of stored body glycogen, protein, and fat in Benedict's subject. **c** Simulated changes of body fat and fat-free masses in Benedict's subject. **d** Simulated body composition changes in the average obese subject during starvation

was lost in the obese subjects compared to Benedict's lean subject requiring an additional cumulative energy imbalance of 17,000 kcal. This amounts to more than 500 kcal/d corresponding to the increased energy expenditure of the obese men.

22.8 Limits of Prolonged Starvation

Of course, starvation cannot proceed indefinitely without severe physiological repercussions. The survivable length of starvation has been attributed primarily to the body fat reserves and the ability of these reserves to spare functionally important body protein. For a period of time in the 1960s and 1970s, starvation became a popular treatment for obesity and regularly involved fasts of many weeks (Drenick et al. 1964; Thomson et al. 1966). The longest known period of therapeutic fasting was published in 1973 when a 27-year-old man weighing 207 kg fasted continuously for a period of 382 days losing 125 kg (Stewart and Fleming 1973). Clearly, such a prolonged fast would be impossible for a lean subject such as Levanzin since his body contained insufficient energy stores. As body fat becomes depleted, the only remaining fuel source is the functionally important

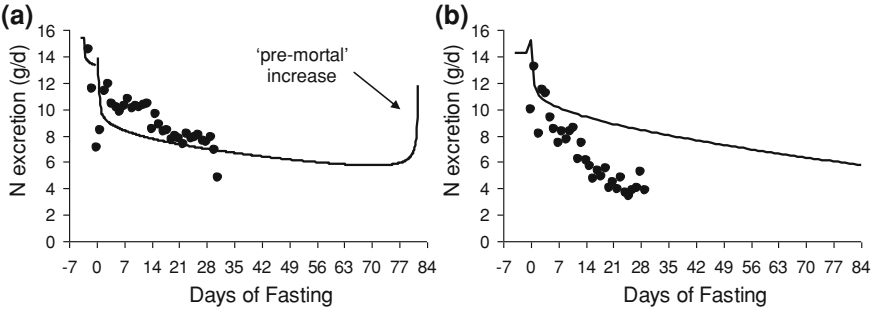

Fig. 22.7 **a** Measured nitrogen excretion rate (●) during starvation in Benedict's lean subject. Model simulation of an extended 82-day period of starvation reveals a predicted premortal increase of nitrogen excretion (*curve*) indicating the physiological limits of starvation. **b** Average nitrogen excretion during starvation in obese men (●) illustrating greater nitrogen sparing compared to the model simulations (*curve*) with no indication of a premortal increase of protein catabolism after 82 days

body protein, whose mobilization results in a classic tell-tale sign of impending death—the 'premortal rise' of nitrogen excretion (Lusk 1976).

Figure 22.7a depicts the simulated nitrogen excretion in Levanzin's fast showing a reasonable agreement with the measurements. Extending the simulated fast to 82 days when the body fat becomes depleted resulted in a premortal rise of nitrogen excretion coinciding with a rapid increase in body protein catabolism to meet energy needs. This simulation suggests that 82 days was the upper limit of a survivable fast for such a lean subject (Fig. 22.7a). Of course, many other factors could claim such a person's life well before this upper limit, and people engaged in hunger strikes have certainly died on a more abbreviated time frame (Leiter and Marliss 1982). Figure 22.7b illustrates a simulated 82-day fast in obese men and shows that nitrogen excretion remained low since body fat was still far from being depleted in these men. Interestingly, the measured average nitrogen excretion over the 30-day fast was significantly lower than the model simulations, suggesting that the current computational model does not completely simulate the nitrogen sparing mechanisms observed in obese subjects (see also Harlow, Chap. 17). Addressing this apparent model deficiency will be a subject of future work.

22.9 Summary

The computational model of human macronutrient metabolism highlighted in this chapter simulates the myriad of metabolic adaptations that occur in response to starvation, including the rapid switch from predominantly carbohydrate oxidation toward fat oxidation and a concomitant increase of ketone production to supply the brain with its energy needs. The model also illustrates how metabolic rate slows

out of proportion to weight loss during starvation and thereby reduces the body's overall energy needs—an adaptation that works to oppose the weight loss that is so often a desired in an increasingly obese world.

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