Obesity

Resting Energy Expenditure: From Cellular to Whole-Body Level, a Mechanistic Historical Perspective

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The basis of heat generated by the human body has been a source of speculation and research for more than 2,000 years. Basal heat production, now usually referred to as resting energy expenditure (REE), is currently recognized as deriving from biochemical reactions at subcellular and cellular levels that are expressed in the energy expended by the body's 78 organs and tissues. These organs and tissues, and the 11 systems to which they belong, influence body size and shape. Connecting these subcellular-/cellular-level reactions to organs and tissues, and then on to body size and shape, provides a comprehensive understanding of individual differences in REE, a contemporary topic of interest in obesity research and clinical practice. This review critically examines these linkages, their association with widely used statistical and physiological REE prediction formulas, and often-unappreciated aspects of measuring basal heat production in humans.

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Study Importance

What is already known?

- Measurements and predictions of basal metabolic rate or closely related resting energy expenditure are widely used in the study and clinical management of adults with obesity.
- Vast knowledge of the mechanisms leading to basal heat production in humans has been acquired by investigators working in basic and clinical research areas over the past century.
- A synthesis connecting these diverse observations with common adult phenotypes is lacking.

What does this review add?

- This review integrates mechanisms at the cellular and organ-tissue body composition and functional levels with variation in body size and shape.
- Combining these integrated mechanisms with a person's age and race/ethnicity provides a new basis for understanding individual differences in basal heat production in adults.
- This review also critically examines newer concepts related to the influence of ongoing weight loss and subsequent weight maintenance on basal heat production.

Historical Overview

On the eve of the French Revolution in 1789, Antoine Lavoisier and his coworkers published their findings likening heat production in animals and humans to "combustion" in a candle: uptake of oxygen and release of heat, carbon dioxide, and water (1). The candle's flame is extinguished when its combustible matter, or mass, is exhausted. One century later, in 1895, an astute observer, Adolf Magnus-Levy, surmised that combustion accounted for the weight loss that a woman with obesity experienced when his colleagues treated her with thyroid tablets (2). Magnus-Levy tested his hypothesis by administering thyroid tablets to a nurse with obesity while monitoring whole-body oxygen consumption over the course of 3 weeks (2). His hypothesis proved correct: the nurse's oxygen consumption increased by 30%, proving that thyroid extract stimulates metabolism and heat production in humans. Recognizing the relevance of his observation, Magnus-Levy went on to show that myxedema was accompanied by a metabolic rate almost half that of normal, a state he corrected by administering thyroid extract (2). Protocols for evaluating a person's oxygen consumption were not yet standardized in the late 19th century, prompting Magnus-Levy to recommend strict conditions for measuring "Grundumsatz," or basal metabolic rate (BMR), in 1899 (2,3). Measuring BMR soon became the widely accepted tool for diagnosing thyroid diseases and monitoring the effects of treatment.

Four decades later, so much knowledge had accumulated on the topic of human energy expenditure that Eugene F. Du Bois devoted his entire 494-page classic book, published in 1936, to "Basal Metabolism in Health and Disease" (4). By then, "thousands" of indirect calorimeters had been installed at medical centers throughout the world, including major institutions such as Mayo Clinic (4). Diagnosing and monitoring diseases such as hypo- or hyperthyroidism required setting standards for "normal" BMR, and most workers at the time agreed that values within ± 10% of predictions based on body surface area were an acceptable range. People with diseases such as acute hyperthyroidism, as shown by Magnus-Levy (2), had BMR of 80% to 100% above those predicted for their age, sex, and body size.

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Indirect calorimeters have long since been replaced by sensitive blood tests for diagnosing thyroid and other metabolic diseases. Yet BMR, or more commonly, resting energy expenditure (REE), is as relevant today as it was when Du Bois published his book in 1936 (4). Countless BMR and REE estimates are made every day by people across the globe to derive energy requirements. Physiology and clinical research laboratories include REE measurements as part of numerous applied and basic research projects. REE measurements are often predicted using statistical approaches (e.g., regression analysis), such as applying the Harris-Benedict equations (5) reviewed in detail by Du Bois 8 decades ago (4). Are there new ideas on ways to predict BMR and REE beyond statistical models? Could we use equations such as those reported by Harris and Benedict as a window through which to view the cellular and organ-tissue determinants of BMR? How far have we come in explaining individual differences in BMR beyond the "± 10%" suggested in 1936 by Du Bois (4)? Is BMR influenced by variation in energy balance? This review examines these questions, with a focus on adults, beginning with an overview of relevant measurement conditions and mechanisms underlying heat production.

Measurement

Magnus-Levy's concept of BMR was that it represents the "metabolism required for the conservation of normal functions while the organ activity is eliminated as much as possible" (2). Strict measurement conditions were established to minimize variation in energy expenditure owing to technical measurement errors, extraneous participant stimulation, and even movement during the test. The extent to which these rigorous conditions were met is embodied in the classic study by Harris and Benedict (5), who reported in 1918 that evaluated participants were in "perfect muscular repose" as "assured by an automatic record of all movements, even those imperceptible to a trained observer." Early studies often included multiple measurements on the same day in each participant with extreme values excluded from results (4).

Magnus Levy and others set ambient temperature during BMR measurements within the thermoneutral range of ~21°C-27°C so that internal temperature regulation in the lightly clothed person was maintained by dry heat loss and not by sweating or non-shivering thermogenesis (6). As with imperceptible body movements, "thermal comfort" effects related to age, sex, body composition, and clothing are now recognized as factors that can have a subtle influence on a person's REE (6,7). A recent proposed approach is to track skin blood flow before and during energy expenditure studies as a means of monitoring vasoconstriction-vasodilation responses that signal challenges to core temperature stability (6,7).

BMR does not represent the nadir in 24-hour heat production. Minimum levels of arousal and movement are reached during stage 3 sleep (8), with sleeping metabolic rate tending to be lower than early morning awake metabolic rate by about 5% (9). BMR also varies during the ovulatory cycle in women, with higher energy expenditure (~7%) in the luteal phase that begins following ovulation compared with the follicular phase that starts with menstruation (10). A portion of the increase in heat production during the luteal phase of the menstrual cycle can be accounted for by a small rise in core temperature (0.27°C) (10); a 1-°C elevation leads to a 13% increase in energy expenditure (11).

Other causes of variability in resting heat production estimates include training effects (12), technical measurement errors (12-14), indirect calorimetry equipment and calculation differences (12), and intra-individual variation over time. The use of standardized measurement conditions showed that intra-individual variability over days or months in REE is relatively low (15). Johnstone et al. (14) measured postabsorptive energy expenditure three consecutive times in the morning and found that only 2% of the observed variability was attributable to within-individual effects, a portion of which (0.5%) was analytic error. Bader et al. (16) reported an intra-individual coefficient of variation (CV) for REE of 5% measured over time periods extending up to 6 months that also included measurement error. Schoffelen and Plasqui (17) reported the highest reproducibility for sleeping metabolic rate (CV, 2.4%) measured in a respiratory chamber with a larger CV (3.3%) for BMR evaluated using a ventilated hood indirect calorimeter.

Today, the term "BMR" is largely reserved for measurements made under the strict conditions reported in classical metabolic studies. The term "REE" encompasses a wider range of reported measurement conditions (18), although in some published reports REE is used synonymously with BMR.

Mechanisms

Now in the third century since Lavoisier's seminal discoveries (1), the mechanisms leading to basal heat production in humans are largely understood at the subcellular, cellular, and organ-tissue levels, although important gaps remain. The sections that follow provide an overview of these mechanisms, gaps in current knowledge, and potential future research areas.

Cellular level

By the end of the 19th century, it was understood that three organic substrates in the diet, protein, fat, and carbohydrate, were oxidized *in vivo* with release of CO_2, H_2O, N, and heat (19). The decades that followed established the mechanisms by which the three primary metabolic fuels are transformed to usable forms of energy at the subcellular and cellular levels. The first step is ingestion of metabolic fuels as components of food, and about 95% of this ingested energy is retained (20). Another 4%-5% is lost in the urine as urea and other nitrogenous compounds, the end products of protein metabolism. The remaining ~90% is available for cell metabolism and accounts for whole-body oxygen consumption and heat production (Figure 1). The estimates that follow were derived from a variety of studies, including *in vitro* experiments (21).

Of the metabolizable energy available after accounting for fecal and urinary losses, the majority is processed by cells via the Krebs cycle in mitochondria. A relatively impermeable inner mitochondrial membrane is separated from a porous outer membrane by an intermembrane space. Krebs cycle enzymes located on the inner mitochondrial folds, or cristae, generate ATP via oxidative phosphorylation. During this process, protons are pushed across the inner mitochondrial membrane into the intermembrane space, creating an electrochemical gradient that powers conversion of chemical energy in metabolic fuels to ATP. This process is tightly coupled, although partial uncoupling of substrate oxidation to ATP generation releases heat that largely accounts for REE (21). Two components of

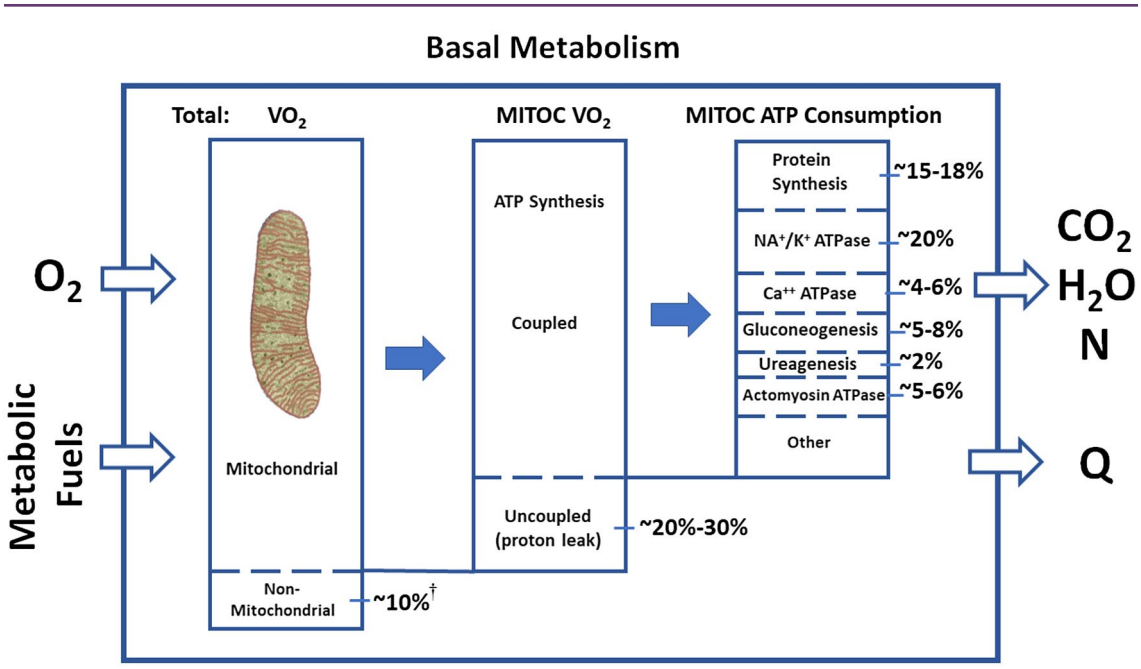

Figure 1 Energy utilization at the cellular level in the basal state. †While most cell oxygen consumption and energy generation culminate with ATP synthesized in mitochondria, about 10% of respiratory oxygen uptake supports the actions of miscellaneous tissue oxidases (21). For example, oxygenase enzymes in the brain incorporate molecular O_2 into hydroxyl groups when synthesizing neurotransmitters such as norepinephrine and serotonin. Modified from Rolfe and Brown (21). MITOC, mitochondria; N, nitrogen; Q, heat; VO_2, oxygen consumption.

mitochondrial heat generation are recognized: a basal proton leak that accounts for up to 20%-30% of oxygen consumption and is thought to affect whole-body energy utilization and inducible proton leaks that play a role in the heat generated by brown adipose tissue (21). Uncoupling of ATP synthesis is a feature of brown adipocytes, but the consensus is that basal heat production by brown adipose tissue in thermoneutral environments is relatively small in adults (22,23). Proton leakage is observed in other tissues, including skeletal muscle, liver, kidneys, and brain (21). The recent discovery that sarcolipin (a transmembrane proteolipid that regulates several sarcoplasmic reticulum Ca^{++}-ATPases in skeletal muscle) may be related to non-shivering thermogenesis highlights the potential role of other heat-loss mechanisms that may be activated under some circumstances (24).

There are other pathways outside of the mitochondria that consume or produce smaller amounts of ATP. For instance, some ATP is generated outside of mitochondria during glycolysis, an oxygen-independent pathway in which glucose is converted to pyruvate in the cytosol. Other subcellular organelles also contribute to overall energy expenditure, although they have a small role. For example, lysosome v-type ATPases maintain H+ ion gradients in order to sustain the low pH required for the optimum function of some hydrolases (25).

The ATP generated by mitochondria are distributed across multiple cellular processes required for maintenance of basal metabolic functions (Figure 1). Three biosynthetic pathways consume almost one-third of available ATP, the largest of which is protein synthesis (~15%-18%) followed by gluconeogenesis (~5%-8%) and ureagenesis (~2%) (21).

Another one-third of ATP is consumed in reactions involving membrane ATPases (21). These enzymes dephosphorylate ATP and release energy needed for basal cellular processes. The three major classes of ATPases, NA^+/K^+, Ca^{++}, and actomyosin, account for ~20%, ~4%-6%, and ~5%-6% of basal mitochondrial ATP consumption and heat production, respectively (21). The functional tasks of these ATPases include maintenance of cellular osmotic equilibrium, electrochemical gradients, muscle tone, and other related activities.

Cellular-level processes are moderated by hormones, some of which directly influence thermogenesis (26). Notably, multiple cellular activities involved in thermogenesis are regulated by thyroid hormone (26,27).

Organ-tissue level

The oxygen-consuming cellular reactions described in Figure 1 are reflected in the basal heat production rates of brain, heart, liver, and other organs and tissues. Our current understanding of these rates evolved through a combination of animal and human investigations conducted over the past century. In 1907, the English scientist Joseph Barcroft began reporting a series of catheterization studies aimed at estimating the mass-specific metabolic rates (*Ki*) of major organs and tissues (28). Publishing studies in dogs 1 year later, Barcroft found that "summated" tissue metabolism (29) could explain 83% of the animal's resting oxygen consumption. Field and colleagues later reported in 1939 that cumulative *in vitro* tissue respirations could account for 89% or more of an albino rat's REE (30). Drabkin and Jean in 1950 (31) reported basal oxygen consumption estimates for human brain, heart, liver, kidneys, and skeletal muscle, and by 1992, accumulated findings led Elia to propose *Ki* values for most major

Organ	Mass (kg)	*Ki* (kcal/kg/d)	Energy Expenditure (kcal/d)	(%REE)
	M/F		M/F	M/F
	1.60/1.43	240	384/343	21/20.0
	0.30/0.27	440	132/119	7.2/6.9
	0.33/0.28	440	145/123	7.9/7.2
	1.68/1.50	200	336/300	18.4/17.5
	30.6/21.3	13	398/277	21.7/12.7
	19.3/29.6	4.5	87/133	4.8/7.6
	87.0/76.5	21.0/19.7	1810/1469	100/100

Figure 2 Mass-specific metabolic rates (*Ki* values) of selected organs and tissues (32) and the whole body. Selected data for males and females (M/F) from a previously reported study (33) (Supporting Information) were used to estimate mass, resting energy expenditure (REE), and percentage of daily REE. Age, weight, height, and BMI of the sample were (M/F): 45.3/40.4 years; 87.0/76.9 kg; 179/167 cm; and 27.3/27.3 kg/m^2.

human organs and tissues (32) (Figure 2). Combining these estimated *Ki* values with corresponding organ and tissue weights provided a means by which a person's REE could be calculated as the sum of major organ and tissue REEs. According to this approach, an organ or tissue's REE is the product of its estimated *Ki* value and mass. For example, the heart's *Ki* value was estimated by Elia as 440 kcal/kg/d, and thus the average 300-g organ is predicted to consume 132 kcal/d or roughly 10% of a person's REE.

Noninvasively measuring the volume and mass of most body organs and tissues with magnetic resonance imaging (MRI), without undue radiation exposure, became feasible in the late 1990s. Gallagher et al. in 1998 (34) and Illner et al. in 2000 (35) combined MRI-measured organ and tissue volumes with Elia's *Ki* values to achieve proof of concept in humans by demonstrating close agreement (mean Δ, 1%-2%) between summated organ and tissue mass heat production rates and REE in healthy adults. Their physiological modeling approach was straightforward: each major organ and tissue volume was measured with MRI and converted to mass using assumed stable tissue densities; the energy expenditure of each organ and tissue was next calculated as the product of Elia's *Ki* value and measured mass; and REE was then calculated by summing the individual organ and tissue REEs. An example of these calculations is shown in Figure 2 for a demonstration sample consisting of healthy adults reported in a previous study (33) and whose characteristics are summarized in Supporting Information I. A person's whole-body *Ki* can be derived as their measured or calculated REE divided by their body weight (Wt), and these *Ki* values are given in the figure for men and women and in Table 1 for Reference Man and Reference Woman (33,36).

The energy costs of physiological processes regulated by the autonomic nervous system are incorporated into the estimated organ and tissue *Ki* values as reported by Elia (32). These homeostatic activities include heart rate, blood pressure, glomerular filtration, respiratory activity, peristaltic actions, and many other actions that moderate basal oxygen consumption. An example of their impact on organ *Ki* values can be appreciated using the rate-pressure product relationship for heart, myocardial oxygen consumption ∝ heart rate × systolic blood pressure (37). During sleep, heart rate and blood pressure reach a nadir at about 3 AM, resulting in a *Ki* value that is markedly lower than in the awake state (38). That is one of several similar physiological responses that lead to a lower sleep REE than awake REE measured in the early morning.

Despite tremendous progress made over the past century, our ability to measure REE at the organ-tissue level remains limited. First, there is a critical need for methods that can quantify actual *Ki* values *in vivo* across most organs and tissues. As a result of this limitation, current physiological models incorporate estimated *Ki* values for some major organs and tissues, but none are recognized for components such as the gastrointestinal tract and lung. Instead, tissues for which no *Ki* value exist are frequently lumped into a large "residual" component that is then assigned an estimated *Ki* value; however, this introduces a source of error into REE estimation. A second limitation is that whole-organ volumes evaluated with MRI cannot account for non-metabolically active components such as blood, connective tissue, and fat that can be present in variable amounts in skeletal muscle, liver, and other organs (39). This variance can influence an organ's density, a value now assumed constant when converting MRI-measured volumes to mass. Third, published *Ki* values may not accurately account for regional differences in oxygen consumption that occur within some organs and tissues, such as the brain (40). The same likely applies to adipose tissue, a highly diverse tissue located in different anatomic sites throughout the body (41,42). Lastly, as we review in a later section, *Ki* values are age specific, and information is only now emerging on mass-specific organ metabolic rates that apply across the life-span (43-45).

Whole-body level

Weight. Wt, or mass, represents the sum of all cellular and organ-tissue-level heat-generating components and a relatively small amount of metabolically inert matter such as hair, tendons, and extracellular connective tissues. The relationship between REE and body mass is a defining feature of mammals, including humans, and is articulated in Kleiber's Law, $REE \propto Wt^{0.75}$ (46). Accordingly, Wt is the primary REE predictor variable at the whole-body level and makes up a key component of modern prediction equations, the most enduring of which were reported by Harris and Benedict in 1918 (5),

$$\text{Men: } REE = 66.5 + (13.75 \times Wt) + (5.003 \times \text{Height}) - (6.755 \times \text{Age})$$

$$\text{Women: } REE = 655 + (9.563 \times Wt) + (1.850 \times \text{Height}) - (4.676 \times \text{Age})$$

with REE, Wt, height, and age in kilocalories/day, kilograms, centimeters, and years, respectively. This classic equation provides a window into the underlying structural factors, the organs and tissues that account for a person's basal rate of heat production. For example, questions such as why height and age are included in these equations, why there are separate equations for men and women, and why these equations predict REE values for African Americans that are systematically lower than those measured (38) can be answered by exploring how body size measures such as weight and height translate to organ-tissue-level heat-producing units of the human body. This approach provides a mechanistic basis at the organ-tissue level for statistical whole-body REE prediction equations such as those reported by Harris and Benedict (5).

TABLE 1 Composition and REE of reference man and woman†

	Mass (kg)		% of Mass		% of REE		% ATFM	
Component	Man	Woman	Man	Woman	Man	Woman	Man	Woman
Adipose tissue	15	19	21.4	32.8	4.0	6.3		
Skin	2.6	1.8	3.7	3.1	1.1	1.0	4.7	4.6
SM	28	17	40	29.3	21.7	16.4	50.9	43.6
Bone	10	6.8	14.3	11.7	1.4	1.2	18.2	17.4
Heart	0.33	0.24	0.47	0.34	8.7	7.8	0.60	0.62
Liver	1.8	1.4	2.57	2	21.5	20.8	3.27	3.59
Kidneys	0.31	0.28	0.44	0.39	8.1	9.1	0.56	0.72
Spleen	0.18	0.15	0.26	0.21	1.1	1.1	0.33	0.38
Brain	1.4	1.2	2.00	1.71	20.0	21.3	2.55	3.08
Residual	10.4	10.1	14.9	17.4	12.4	15.0	18.9	25.9
Total	70	58	100	100	100	100	100	100

Residual mass is the difference between body weight and the sum of the nine other measured organs and tissues.
ATFM, adipose-tissue free mass; *Ki*, mass-specific metabolic rate; REE, resting energy expenditure; SM, skeletal muscle.
† From Snyder et al. and Hwaung et al. (33,36).

The human body has 78 organs, and yet remarkably, they and the 11 systems they compose are relatively stable proportions of Wt across normal-weight adults. That's one reason why Reference Man and Woman have similar respective whole-body *Ki* values (i.e., REE/Wt) of 24.3 and 23.6 kcal/kg/d (Table 1) and why REE is highly correlated with body mass in adults, as it is in our demonstration sample (men/women; R^2, 0.69/0.72; both $P<0.001$). All adults, in effect, are largely designed the same way, which is why body mass accounts for more than two-thirds of interindividual differences in REE. This concept is captured in Pelley's prediction equation (47), REE (kilocalories/day)=24×Wt (kilograms) for adults whose weights are within the normal body mass index range.

However, deviations from these stable organ and tissue proportions are recognized, and hundreds of scientific papers spanning more than a century have tried to explain the remaining one-third of "missing" variance. A small proportion of this variability is accounted for by technical measurement factors and fluctuations in REE over time in the same person, owing to biological factors such as the menstrual cycle in women or changes in energy balance, as discussed in a following section. Dozens of statistical equations such as those reported by Harris and Benedict (5) have been published linking REE and factors beyond Wt. By inference, these factors signal that organ and tissue proportions, and perhaps their cellular makeup and activity, vary beyond that prescribed by total body mass according to a person's level of adiposity, stature, age, and other measurable characteristics.

For example, men have a higher REE than women, and most of this difference is accounted for by a larger body mass in men. However, adding sex as an REE predictor in our demonstration sample regression model with weight as a covariate increases R^2 from 0.67 to 0.80. The slope of the sex covariate is 220 kcal/d, the predicted difference in REE between men and women at the same weight. The differing associations between REE and body mass in men and women is one reason why published REE prediction equations that include weight as a covariate are often sex specific. Why are these sex differences in REE present after controlling for body mass, and what do they reveal about differences in organ and tissue proportions that exist in men and women?

Before continuing, it is important to note that, in the remainder of this review, we use the term "adipose tissue" rather than "fat mass" unless otherwise specified in a cited publication. Body fat is largely composed of triglyceride (48), and fat-free mass (FFM) includes the cellular portion of adipose tissue, or metabolically active adipocytes, along with the 77 other organs and tissues. Methods such as MRI quantify adipose tissue, while dual-energy x-ray absorptiometry estimates fat mass (42). Adipose-tissue free mass (ATFM) and FFM are calculated as the difference between Wt and adipose tissue and fat mass, respectively.

A woman at the same weight as a man has a larger relative amount of adipose tissue and a smaller proportion as the remaining ATFM. If we replace body mass in our REE prediction model with adipose tissue and ATFM, R^2 increases further from 0.80 to 0.82, and the slope of the sex covariate decreases from 220 kcal/d to 110 kcal/d. ATFM includes 77 of the body's remaining 78 organs and tissues, so we need to narrow down which ones might account for the residual REE differences between men and women described by our model. One potential factor is muscularity since androgens present in men are well-recognized moderators of skeletal muscle mass and function (49). Another is sex differences in brain mass; on average, absolute brain mass is 100-200 g smaller in women, relative to men (50), although as a percentage of ATFM, brain mass is larger in women (Table 2). At the same ATFM, women are thus predicted to have less skeletal muscle and more brain mass than men. Consistent with this conjecture, ATFM has a *Ki* value of about 30 kcal/kg/d in Reference Man and 33 kcal/kg/d in Reference Woman. Accordingly, when we replace ATFM in our REE prediction model with skeletal muscle and brain mass, R^2 increases further from 0.82 to 0.84, and the sex covariate is no longer significant with a slope of 35 kcal/d. Adding the remaining organs that compose ATFM shown in Figure 2 to the model increases R^2 further to 0.87, with all terms significant except bone, spleen, and skin mass; the intercept of this model is 3.0 kcal/d (P=nonsignificant). The proportions of adipose tissue, skeletal muscle, brain, and perhaps other organs and tissues and the REE they determine thus differ between men and women who weigh the same amount. That is the main reason why REE equations at the whole-body level are sex specific and why statistical REE prediction

TABLE 2 Age, body size, and REE of Reference Man (RM) and Woman (RW)†

	RM	RW
Age (y)	25	25
Weight (kg)	70	58
Height (cm)	170	160
REE (kcal/d)*	1711	1389
Ki (kcal/kg/d)	24.4	23.9

†From Snyder et al. and Hwaung et al. (35,36).
*For consistency, resting energy expenditure (REE) was calculated using the Harris-Benedict equation (5).

formulas replacing weight with adipose tissue mass and ATFM should ideally be sex specific.

Height. Our focus so far has been on body mass as a measure of a person's size. The study of basal heat production across people differing in size would be much simpler if all humans were spherical in shape and had the same proportions of all 78 organs and tissues. In fact, there are large between-individual differences in body shape, the most notable of which is variation in height after controlling for weight. If a person's hypothetical weight is kept constant while stretching their length, their shape will change as well as the proportions of their organs and tissues. Brain mass, for example, differs minimally across people who are short and tall and who are the same age and sex (50). At the same weight, a tall person will have much less adipose tissue than a short person of the same age and sex. Skeletal structure is strongly influenced by stature according to well-defined biomechanical "rules" (51). If we add 10 cm to Reference Man and Reference Woman's height while holding their weight and age constant (Supporting Information II), their whole-body respective *Ki* values increase from 24.4 and 23.9 kcal/kg/d to 25.2 and 24.3 kcal/kg/d or about 30-50 kcal/d. Thus, after controlling for weight, a person's height has a significant but small effect on REE, reflecting the net of these as-yet not well characterized organ-tissue effects. For this reason, height is second only to Wt as a covariate in published statistical REE prediction equations (52,53).

Age. Magnus Levy first measured his REE at age 26 and again when he was 76 years old (54). His REE, adjusted for body surface area, had declined by 13% over the 5 decades. Magnus Levy also reported that Benedict, Du Bois, and other pioneers experienced similar reductions in REE as they aged. Since then, many studies ranging from cellular to organ-tissue levels have identified underlying mechanisms leading to reductions in basal whole-body oxygen consumption and energy expenditure with aging.

With increasing age, there are reductions in red blood cell membrane NA^+/K^+ ATPase activity (55); skeletal muscle myosin heavy chain and mitochondrial protein synthesis rates (56); number of liver mitochondria (57); liver, heart, and skeletal muscle mitochondrial respiratory chain capacity (57); tissue β-adrenergic receptors (58); and increases in the rate of mitochondrial proton leakage in skeletal muscle (56). These and many other mechanisms at the cellular level may account, in part, for the lower basal oxygen consumption and energy expenditure rates observed in the elderly.

At the organ-tissue level, most organs decrease in mass over the adult life-span, an effect of aging masked in part by weight stability brought about by an increase in adipose tissue mass (52,53,59,60). That is part of the reason why the elderly have a lower REE than their young counterparts of the same weight and height; adipose tissue has a much lower *Ki* value than most lean tissues (Figure 2). Another factor that affects whole-body *Ki* is the proportional makeup of organs; not all organs lose mass to the same relative extent with aging. Some organs, such as the heart, can increase in mass secondary to underlying common medical conditions, such as high blood pressure (52,59,60). The smaller mass of most organs in the elderly is accompanied by histologic changes that affect REE. For example, microscopic examination of skeletal muscle from older adults reveals an increase in intermuscular adipose tissue, connective tissue, and a smaller number of contractile fibers, notably type 2 (fast-twitch) fibers (61).

These combined cellular metabolic and histologic changes that accompany aging also appear to impact organ *Ki*. In 2010, Wang et al. (62) examined *Ki* values using a regression analysis approach in 131 healthy adults whose major organs and tissue volumes were measured with MRI. Overall, *Ki* values in elderly adults were about 3% below those of younger adults (e.g., 194 and 233 kcal/kg/d for liver and brain vs. 200 and 240 kcal/kg/d). Geisler et al. (60) came to a similar conclusion in 2016. The proportion of brain gray matter (*Ki*, 163 kcal/kg/d) decreases with age relative to white matter (*Ki*, 76 kcal/kg/d), an observation consistent with a reduced whole-brain *Ki* in older adults (60). Although results are inconsistent, brain cerebral metabolic rate of oxygen, measured with multiple different methods and expressed per unit mass of tissue, appears lower in the elderly, notably in specific regions (63).

Cellular, metabolic, histologic, and anatomic changes thus appear to largely account for the lower REE observed in elderly adults. The magnitude of these effects at the clinical level can be estimated with some simple calculations. Here, we start with Reference Man and Woman at age 25 years. Five decades later, their respective *Ki* values would decline from 24.4 kcal/kg/d and 23.9 kcal/kg/d to 21.6 kcal/kg/d and 19.6 kcal/kg/d (Supporting Information II), a reduction of about 10% to 15%. This is about the same magnitude of REE lowering experienced by Magnus-Levy between the ages of 26 and 76 years (47). An even more striking decrease in REE with age was reported by Muller et al. (64), who observed a peak mass-specific REE of FFM of 25.6 kcal/kg/d in growing prepubertal children and a level more than half that in people over the age of 80 years at 12.0 kcal/kg/d.

Adiposity and muscularity. Our review so far on how body size, shape, and composition relate to REE has focused on generalities describing people who have a relatively "normal" Wt. But what happens to REE when Wt increases beyond what is considered the normal range based on a measure such as BMI? Under these conditions, the "growth" in body mass can take two main pathways: growth of the adipose tissue compartment during and after a period of positive energy balance; and growth of the skeletal muscle compartment during and after a period of increased physical activity levels. The effects on REE would be simple to describe if the gained weight consisted solely of adipose tissue or skeletal muscle mass, although that does not occur. To understand how "growth" of body mass in adults influences body composition, we frame this discussion

in the context of the evolutionary biology hypothesis referred to as symmorphosis (45). According to the symmorphosis hypothesis, organisms are "economically" evolved to accommodate maximal metabolic and mechanical demands without energetic inefficiencies brought about by carrying "excess" structure. The symmorphosis construct states that structures and functions of organs are adaptable to the loads placed on them, the effects are coordinated across systems, and responses are optimized to maximize energetic efficiency. This concept provides a roadmap by which we can understand why compartments such as ATFM and FFM are so highly correlated with REE.

Beginning with adipose tissue, functional demands are placed on most body organs and their systems with expansion of this compartment during periods of positive energy balance. To preserve basal homeostatic functions and maintain reserve capacities, many organs adapt by changing their structure and mass. These adaptations are mediated by extrinsic and intrinsic mechanisms and in theory lead to organ structures that perfectly match the demands placed on them (65). In the case of adipose tissue expansion, systemic functional demands lead to coordinated structural effects on skeletal muscles, bones, heart, and other organs and tissues (Figure 3) (65). Systems with multiple organs and tissues are also linked through their functional activities. A large adipose tissue mass with high daily energy expenditure requires coordinated actions across cardiovascular, respiratory, and urinary systems. The main components of "obesity tissue" are skeletal muscle, bone, and visceral organs. Intra-individual responses to weight gain can be heterogeneous, e.g., the myocardium hypertrophies in unique patterns related to varying loading conditions brought about by differing increases in heart rate and blood pressure (59).

While adipose tissue has a *Ki* of 4.5 kcal/kg/d, obesity tissue has a *Ki* of about 10-14 kcal/kg/d, reflecting the combined energy expenditure of these other organ and tissue contributors to REE (36). If we increase Reference Man (70 kg) and Reference Woman's (60 kg) body mass by 25 kg, their predicted REE will increase from 1,711 and 1,389 kcal/d to 2,055 and 1,628 kcal/d, respectively; corresponding whole-body *Ki* values will decrease from 24.4 and 23.9 kcal/kg/d to 21.6 and 19.6 kcal/kg/d (Supporting Information II). The REE increase in people who have obesity is therefore not solely accounted for by an enlargement of the low metabolic rate adipose tissue compartment.

Skeletal muscle has a *Ki* value of 13 kcal/kg/d, higher than that of adipose tissue (4.5 kcal/kg/d) but much lower than that of visceral organs such as liver (200 kcal/kg/d) and heart (440 kcal/kg/d). As with adipose tissue, increases in skeletal muscle impose functional demands on other body compartments such as bone, although we do not have detailed models that describe these effects. Voluntarily building skeletal muscle mass through strength or endurance training increases functional demands that stimulate adaptive responses in heart mass and structure (65,66).

While we do not yet have firm data on the composition of "muscularity" tissue, the implication of these observations is clear: wide between-individual differences in adiposity and muscularity are present in the general population and likely explain part of the observed variability in predicted REE values with equations such as the Harris-Benedict formulas. A relatively large adipose tissue compartment is accompanied by high total-body percentage adipose tissue or fat. Similarly, a relatively large skeletal muscle compartment is accompanied by low percentage adipose tissue or fat. Therefore, one way to improve REE prediction beyond body mass and account for variation in adiposity and muscularity is to add a measure of either percentage adipose tissue or percentage fat. For example, when we add percentage fat to our demonstration sample REE prediction model that includes Wt, R^2 increases from 0.69 and 0.72 to 0.75 and 0.79 in men and women, respectively. This approach has the same effect as modifying the Harris-Benedict equations by replacing Wt with adipose tissue and ATFM or fat mass and FFM. There are many published versions of these statistical REE prediction models that also include age, sex, and other covariates (67,68).

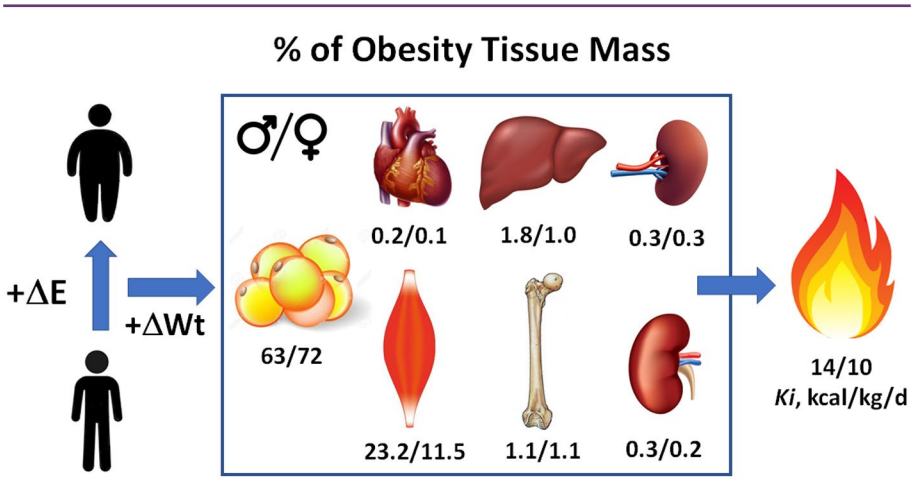

Figure 3 Weight (Wt) gain following a period of positive energy balance includes not only an expanded adipose tissue compartment but also increases in the mass and structure of other tissues and organs, some of which are depicted in the figure. The percentage of "obesity tissue" consisting of these multiple components is shown in the figure for men and women along with the respective mass-specific metabolic rates (*Ki*) of this compartment. The data shown are cross-sectional and are those reported by Hwaung et al. (33). ΔE, energy balance.

We began this section describing body mass as the sum of 78 organs and tissues. As shown in our review, the structures of these many different body compartments and their associated systems are not independent; rather, they follow "rules" that still need refinement and discovery but that we now recognize to be of fundamental importance in defining how sex, stature, age, adiposity, and muscularity relate to REE. Equations for predicting REE such as those reported by Harris and Benedict (5) are useful because they capture these major determinants of coordinated tissue and organ responses at the population level. Similarly, combined compartments such as ATFM and FFM are powerful predictors of REE because tissues and organs undergo a predictable integrated response to variation in loading conditions brought about by fluctuations in adiposity and muscularity across the adult life-span.

Race/ethnicity. Even after controlling for weight, height, and age in the sex-specific Harris-Benedict equations, structural differences between racial/ethnic groups account for a small portion of between-individual differences in REE. The best-documented of these is for African Americans compared with their White American counterparts (69). African Americans have a 5% lower REE compared with people of the same weight, height, and age who are White (69-71). African Americans, on average, have a larger proportion of their weight as skeletal muscle and bone and a smaller proportion as adipose tissue and organ mass than do people who are White of the same body size (69). The racial/ethnic differences in REE are no longer significant when prediction models include body fat, skeletal muscle, and bone mass as covariates (70). The same kinds of REE prediction model differences related to body structure are reported for many other racial/ethnic groups and extend back to studies conducted more than 5 decades ago (72). An important consideration is that factors such as diet, activity levels, and sociodemographic variables can account for some of these previously reported REE and body composition differences between race and ethnic groups.

Genetic mechanisms are now recognized as the basis for some of the individual and group differences in organ size among people who are healthy. One recent example is the adaptive increase in spleen volume present in the Bajau people of Southeast Asia, who live a subsistence lifestyle that includes breath-hold diving (73). The enlarged spleen with greater capacity to hold oxygenated blood improves tolerance to hypoxia and is associated with genetic variants in the *PDE10A* gene (73), a phosphodiesterase linked with thyroid function and spleen size.

Weight Loss Effects

Magnus-Levy, Benedict, Du Bois, and other early investigators were meticulous in their BMR evaluations, including requirements for participants to be weight stable. Today, we can predict a weight-stable person's REE within ± 5%, and organ-tissue prediction models leave only about 10% of the between-individual variance in REE unexplained after considering technical measure factors (74). In current clinical settings, however, prediction formulas are often used to estimate a person's REE and energy requirements during a weight control program or in the "post-obesity" state. These practices raise the question of what effects active weight loss or weight stability in the postobesity state have on REE measurements. Here, we can gain insights into these questions from published studies focused specifically on the temporal sequence of metabolic changes present during and after weight loss. The following observations are based on the longitudinal studies of Muller and colleagues (6,74) conducted in young men residing on a metabolic unit under strictly controlled conditions.

Embarking on a weight loss protocol with a 50% energy deficit led to rapid weight loss in the men (decay constant, X ± SD, −0.78 ± 19 kg/d) (74) that lasted about 3 days, a period referred to as Phase 1 (Figure 4A). By the third day, REE levels were about 50 to 100 kcal/d below those predicted by the group's organ-tissue body composition model (74). The difference between measured and predicted REE is referred to as metabolic adaptation or "adaptive thermogenesis" (75).

Phase 1 was characterized by a sharp drop in plasma levels of insulin and a rise in glucagon, rapid glycogenolysis, and negative energy, nitrogen, sodium, and water balances. Free-water clearance, linked to the fall in insulin levels and an energy-requiring process (76), decreased with excess urinary salt and osmolyte excretion during Phase 1 and is among the physiological adjustments that impact organ *Ki* values, in this case the kidneys. Others have reported REE reductions of similar magnitude with total fasts lasting 24 to 48 hours (77,78).

Weight loss slowed markedly after several days (−0.19 ± 0.03 kg/d), heralding the onset of Phase 2. The slowing of weight loss reflected a transition from mainly decrements in ATFM to a relative increase in lipid oxidation and depletion of fat contained within adipose tissue. By the third protocol week, there were measurable significant reductions in adipose tissue, liver, skeletal muscle, and kidney mass (Figure 4B) that could account for about 60% of the lowering of REE from baseline. The remaining reduction in REE, adaptive thermogenesis, was similar to Phase 1 at 50 to 100 kcal/d. Three factors could account for the magnitude of adaptive thermogenesis at week 3 according to the authors: a significant reduction in glomerular filtration and heart rate/systolic blood pressure that lowered respective kidney and heart *Ki* values, and a decrease in core temperature that impacted whole-body energy expenditure. A recent study by Heinitz et al. (79) reported the presence of adaptive thermogenesis during Phase 2 at weeks 1 and 3 with weight loss of about 100 kcal/d, the same average magnitude as observed by Muller et al. (74). Martins et al. (67) also observed an adaptive thermogenesis level of 90 ± 94.5 kcal/d ($P < 0.001$) after 8 weeks of a 1,000 kcal/d low-energy diet in participants with obesity. Adaptive thermogenesis was no longer significant (26.8 ± 121.5 kcal/d) following 4 weeks of weight stabilization during which the participants gained a small amount of weight.

Active weight loss thus will lower REE on average by about 50-100 kcal/d beyond that estimated using physiological prediction models; in the study by Muller et al. (74), only 60% of participants displayed adaptive thermogenesis at the third week of weight loss. Statistical prediction models will therefore be inaccurate when estimating REE in most people losing weight. Exploration into the basis for this inaccuracy provides insights into the inherent limitations of statistical REE prediction formulas when applied in people losing weight. An extreme example is useful in this regard, examination of the changes in Agostino Levanzin's sleep energy expenditure during his 31-day total fast in 1912 (80). Francis Gano Benedict, who 6 years later with J. Arthur Harris published the now classic Harris-Benedict BMR prediction equations (5), made detailed sleep energy expenditure measurements on Levanzin using both direct and indirect calorimetry systems. Levanzin's weight loss curve and energy expenditure measurements are

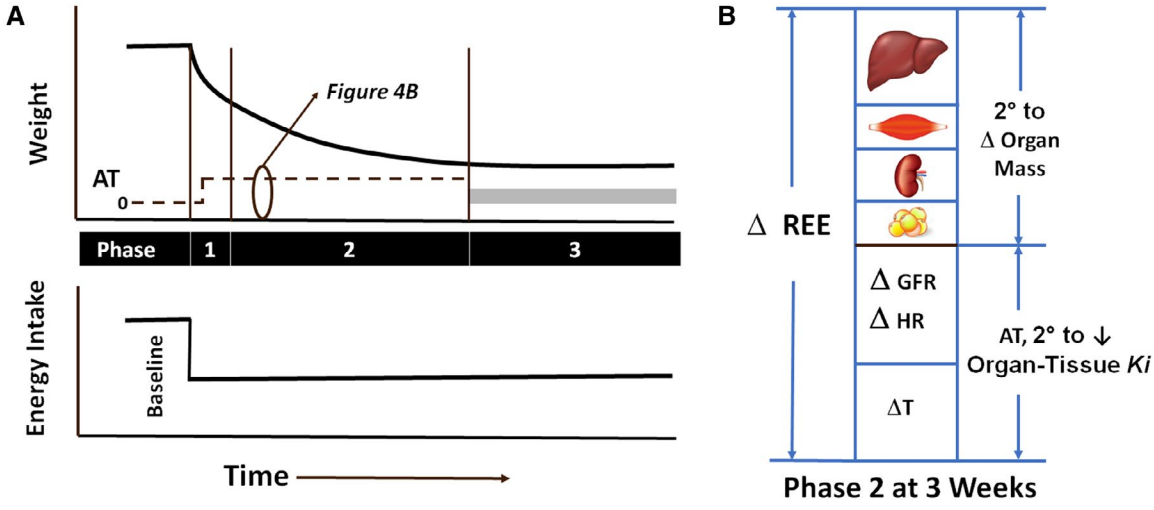

Figure 4 (**A**) Time course of the weight change that follows a reduction in energy intake held at the same lower level until a new steady state is reached. The horizontal gray bar located in Phase 3 reflects the uncertainty in adaptive thermogenesis (AT) magnitude present in the post-obesity state. (**B**) The lowering of resting energy expenditure (REE) observed during Phase 2 following 3 weeks of 50% caloric restriction in men whose weight was in the normal BMI range (74). About one-half of the lowering of REE can be accounted for by reductions in liver, skeletal muscle, adipose tissue, kidney, and brain mass. The remainder is considered AT as reflected in lowering of organ-tissue mass-specific metabolic rate (*Ki*) values. Muller et al. (74) ascribed AT in their study to a slowing of heart rate (HR), reduction in glomerular filtration rate (GFR), and decrease in core temperature (T).

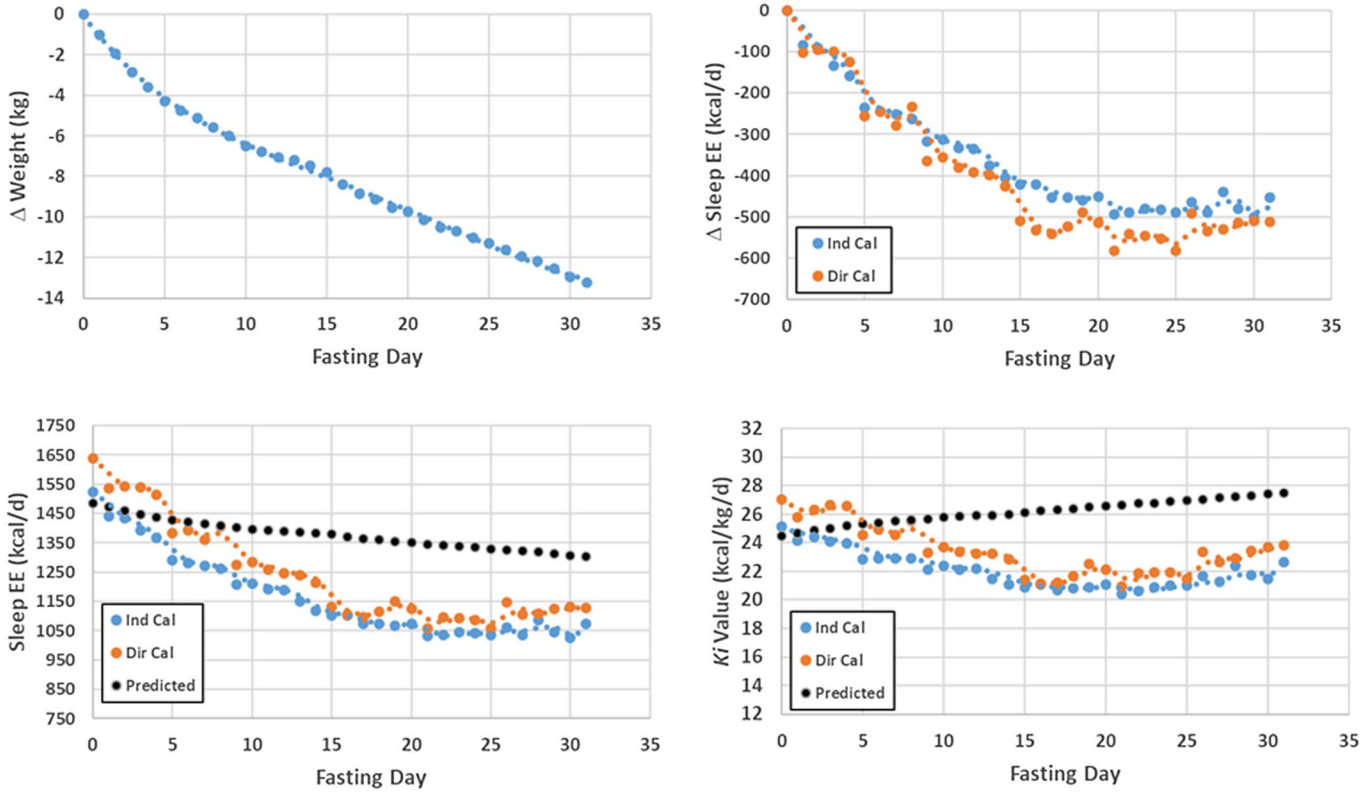

Figure 5 Course of 31-day total fast of Levanzin that was studied by Francis Gano Benedict in 1912 (80). Upper left and right panels show Levanzin's weight and sleep energy expenditure (EE) changes, measured by direct (Dir Cal) and indirect calorimetry (Ind Cal), over the 31-day experiment. The lower left panel shows the actual measured sleep energy expenditure and the predicted basal metabolic rate using the Harris-Benedict equation (5) for men over the 31-day experiment. The lower right panel shows the whole-body *Ki* values (mass-specific metabolic rates) corresponding to the energy expenditure measurements and predictions to the left.

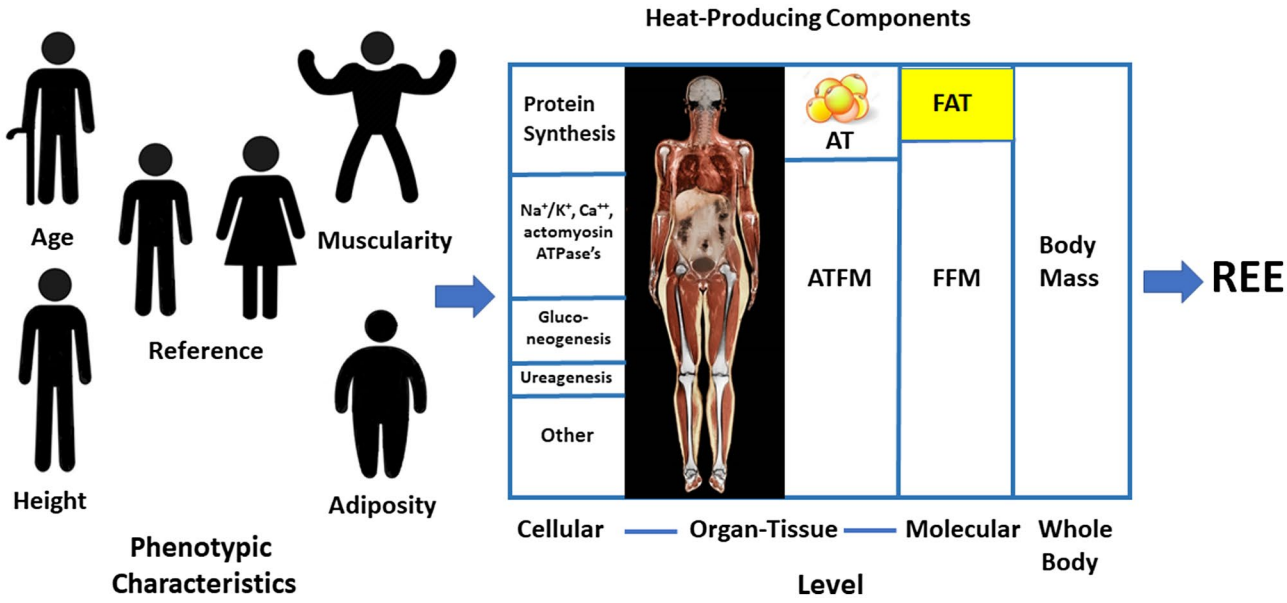

Figure 6 Linkages between common phenotypes and basal heat-producing components of the human body at the cellular, organ-tissue, molecular, and whole-body levels. AT, adipose tissue; ATFM, adipose tissue-free mass; FFM, fat-free mass; REE, resting energy expenditure.

shown in the upper panels of Figure 5. His sleep energy expenditure fell by about 100 kcal/d during the first several days of the fast, largely Phase 1. Weight and energy expenditure continued to decrease during the remainder of the 31-day fast (Phase 2). The Harris-Benedict BMR equation for men increasingly overestimates Levanzin's actual sleep energy expenditure with progression of the fast, as shown in the lower left panel of the figure. The statistical Harris-Benedict BMR prediction equations, in addition to their development in people who were weight stable, link a lower Wt at the same height and age to a lower adiposity level. The Harris-Benedict equation for men thus predicts an increasing *Ki* value as Levanzin loses weight, as shown in the lower right panel of the figure. The Harris-Benedict equation includes the inherent assumption that lower Wt at the same height and age translates to less adiposity tissue and thus higher *Ki* value. Recall from the earlier discussion that increasing adipose tissue is accompanied by a fall in a person's *Ki* value; here, the associations are reversed. By contrast, Levanzin's actual *Ki* values decrease during the fast, a reflection of rapidly changing organ-tissue proportions and their associated *Ki* values (adaptive thermogenesis). Detailed body composition, unavailable to Benedict at the time, would give further insights into the magnitudes of these effects and the level of estimated adaptive thermogenesis. While total fasts are rarely encountered in clinical practice, the kinds of errors described here can be anticipated when applying statistical REE prediction equations to patients with obesity during their weight control program.

Reaching a weight plateau (Phase 3) can take many months to arrive at a new steady state with neutral energy balance and fully remodeled organs and tissues (81). Of the available literature describing metabolic features of people reaching Phase 3, post-obesity, some conclude that predicted and measured REE are approximately equal, whereas others report persistent metabolic adaptations, even during periods of weight regain (25,46,67,68,82-91).

Conclusion

Two thousand years have elapsed since humans first recorded their theories on what produces heat in the human body (19). Two hundred years ago, Lavoisier laid the foundations for modern physiology and metabolism by relating heat production in animals and humans to the processes leading to combustion in a candle (1). Today, we have a deep understanding of basal heat production, including how body size, shape, and composition relate to molecular, cellular, and organ-tissue thermogenesis mechanisms (Figure 6). Nevertheless, large gaps persist, including our inability to quantify many of the involved processes in living humans. Moreover, our REE prediction models remain fragmentary owing to their development using small samples that are homogenous in terms of age, race, and ethnicity, thus lacking the diversity present in humankind. We have yet to fully integrate REE measurements into clinical physiology. Thus, vast future areas of research remain untapped that can fulfill the unrelenting demand for new knowledge on basal heat production mechanisms in humans.O

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