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Special article

The cross-sectional and longitudinal dependence of the resting metabolic rate on the fat-free mass

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Abstract

The dependence of the resting metabolic rate (RMR) on the fat-free mass (FFM) of temporarily fasted well-fed subjects has been studied by many researchers over the years. The results of 10 such studies yield an average linear dependence with a slope of 75 ± 15 kJ/kg per day. In the work of Keys et al (The biology of human starvation. Minneapolis, MN: University of Minnesota Press, 1950) on semistarved subjects, however, the slope of the RMR dependence on the FFM was found to be 280 ± 50 kJ/kg per day. The argument presented in this article is that the result derived for the large group of well-fed subjects is cross-sectional information, whereas that for the semistarved subjects is longitudinal data. The linear regression of the longitudinal data yields a negative offset term that when combined with the RMR vs FFM slope divides the FFM into active and inactive components, active tissue being that which interacts directly with oxygen. The linearity of the RMR vs FFM curve suggests that the elements of the active tissue mass are energetically similar regardless of their distribution in the body's organ systems. The active-inactive model implies that the longitudinal data results from the decrease in active tissue alone, whereas cross-sectional data for different individuals correspond to an admixture of both active and inactive tissue. For different individuals having the average RMR vs FFM slope of the semistarved subjects, it is calculated that a change in the FFM consists of about 27% active and 73% inactive tissue. A histogram of the individual longitudinal RMR vs FFM slopes for the 32 semistarved subjects yields an unexpected non-Gaussian distribution with a minimal value of 158 kJ/kg per day and a maximal value of 405 kJ/kg per day.

1. Introduction

The term *cross-sectional data* refers to static information relating to a group of different subjects, whereas the term *longitudinal data* refers to evolving information dealing with individual members of the larger group usually resulting from a designed experimental change. Depending on the system being studied, longitudinal data need not in general be the same as that represented by the cross-sectional data.

Many experiments have been done over the years to determine the dependence of the metabolic rate on the fat-free mass (FFM). Ten such studies are quoted in this article and are presented in tabular form. These studies often do not measure the same metabolic state. The basal state is defined by a protocol [1] that specifies the periods of rest, fasting, sample collection, and the ambient conditions. When this protocol is relaxed, the resulting metabolic state is often called the resting metabolic rate (RMR). The metabolic state can also be measured during sleep. These metabolic states are all related in their design to avoid including the thermal energy produced by activity and that produced by food digestion, transportation, and deposition. We will hereafter use the general term RMR in a broad sense to include the basal and sleeping states and will later show that these distinctions do not significantly alter our results. The 10 studies quoted in this article give a linear dependence of the RMR on the FFM with an average slope of 75 ± 15 kJ/kg per day. Some of these studies show high correlation coefficient values. All of the quoted experiments were done on temporarily fasted well-fed subjects.

On the other hand, from data provided in the experimental work of Keys et al [1] where 32 young male subjects at the University of Minnesota were put onto a semistarvation diet of 6.56 MJ/d for 24 weeks, a linear longitudinal dependence of the RMR on the FFM was

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calculated to have a slope of 280 ± 50 kJ/kg per day. For purposes of brevity, we will frequently refer to the Keys et al work as the Minnesota experiment (ME).

A possible explanation for the differing slopes of the RMR vs FFM linear regressions for the well-fed (cross-sectional) and energy-deficient (longitudinal) groups is that the RMRs of the latter subjects are increased in value as a result of compensatory or adaptive processes. This view implicitly assumes that the well-fed subjects make up the control group for the energy-deficient subjects. This explanation loses much of its appeal, however, when it is recognized that the well-fed subjects provide cross-sectional information, whereas the underfed subjects should be considered to provide longitudinal data that need not closely agree with the cross-sectional data.

Let us briefly elaborate on the cross-sectional and longitudinal dichotomy suggested in the previous paragraph. The well-fed subjects represent a large, static, and possible diverse population. If we consider a single individual of the static population and restrict the food energy available to that person, we can study the change in the individual subject's RMR or any other time-dependent parameter such as the FFM. In this example, the large static group provides cross-sectional information, whereas that dealing with the single individual is clearly longitudinal. Because human biological parameters are variable, a more realistic experimental procedure would be to include several similarly food-restricted subjects along with the single original subject. Each food-restricted subject provides longitudinal data, and the test group's average results and distributions must also be considered to be longitudinal.

In addition to the large value of the RMR vs FFM slope of the ME, the corresponding offset term that resulted from linear regression analysis was found to have a value of −9994 ± 2000 kJ/d; thus, the average results for the 32 experimental subjects can be specified by 2 numerical parameters.

In this article, we will show that the arithmetic division of the offset term by the slope of the RMR vs FFM linear regression line will give the mass of the inactive tissue. The term *inactive* here means that there is no direct reaction of this tissue with oxygen. The linearity of the RMR dependence on the FFM implies that the inactive tissue mass does not change during semistarvation. This view may not be apparent to the reader. If we consider a hypothetical RMR vs FFM curvilinear dependence and extend tangential lines from various points on the curve to intersect the FFM axis, we would not get a fixed FFM value corresponding to a zero value of the RMR. The suggested constancy of the inactive tissue mass is unexpected and does not agree with the common idea that both active and inactive tissue decrease during semistarvation and also appears to be in conflict with the expected onset of starvation edema that accompanies nearly all cases of severe undernutrition, a paradox that will later be rationalized.

The 2-parameter fit of the RMR vs FFM data has another interesting feature. Considering a single individual whose FFM is changing, the slope of the RMR vs FFM linear regression describes the subject's longitudinal behavior. Changes in the offset term, which can only occur for different individuals, can be related to the cross-sectional data for all those individuals having the same longitudinal dependency. Thus, the 2 parameters indicating the RMR dependence on the FFM are complementary descriptions of both group and individual RMR properties.

We will be able to derive a general equation, in the cross-sectional case, for the fraction of the inactive tissue mass relative to the FFM as a function of the FFM. This equation shows a monotonic increase of this fraction with increasing FFM reaching an asymptotic value of 0.73 ± .23. This value likely corresponds to the sum of the larger aqueous and smaller mineral fractions of the body and may be nearly the same for all individuals.

Ravussin and Swinburn [2], studying data for Pima Indians to identify metabolic predictors of obesity, point out that longitudinal studies are more likely to provide clearer insights into cause-effect relationships than are cross-sectional data. In this article, longitudinal data directly relate the RMR to the amount of active tissue, whereas cross-sectional data give allometric information on both active and inactive components.

Both types of data are significant; however, the longitudinal information yields a more direct casual relation between the RMR and FFM.

2. Theoretical and experimental considerations

The 2-reservoir energy model developed by this author [3] provides the theoretical basis for this work. The human body is divided into the fat mass (FM) and the FFM, and these 2 entities are the repositories of stored energy. The FM is defined as a uniform chemical body made up of fatty acids and glyceryl esters and should not be confused with adipose tissue of which it is the major component. The FFM contains all nonfat ingredients including protein, glycogen, bone mineral, aqueous content, and many other components. The fundamental reason for the adoption of the 2-reservoir model derives from the historical method of measurement of these quantities by underwater weighing. In this model, the RMR is only a function of the FFM.

It is recognized that there are actually 3 energy reservoirs within the body, ie, fat, protein, and glycogen, which correspond to the nature of the food types that can be metabolized. Glycogen, which is mainly found in the muscles and liver and is important in muscular activity, is considered to be part of the FFM as is the much larger quantity of protein. Because the FFM includes both glycogen and protein, the energetic modes of these 2 stores, including their states of hydration, cannot be separated using the 2-reservoir model; however, we will later justify considering the protein to be the major source of energy stored in the FFM mainly because of its dominant mass and ability to store much more energy than glycogen.

When the 2-reservoir energy model is applied to the results of the ME, it is found that the FM decreases exponentially with a time constant of 135 ± 10 days [4]. This experimental result does not support the popular linear model for the decrease of adipose tissue where dietary energy deficits are assumed to come solely from the FM; implicit in the popular model is that the FM has no limit on its ability to provide whatever energy deficit may exist. It can be shown from the exponential decay, however, that the FM is limited in its energy transfer rate to a value of 290 ± 25 kJ/kg per day [4]. This means that if a dietary energy restriction is too severe for the FM to make up the energy deficiency, then the FFM must decrease immediately, demonstrating that the "fat goes first" concept is incorrect. The immediate decrease in the FFM on commencing a semistarvation diet has been graphically illustrated by this author [3,4]. We will later cite experiments where seriously obese subjects were put onto long-term limited-energy rations resulting in a decrease of the FFM. Because the RMR is a monotonic function only of the FFM, the RMR will also decrease in these experiments.

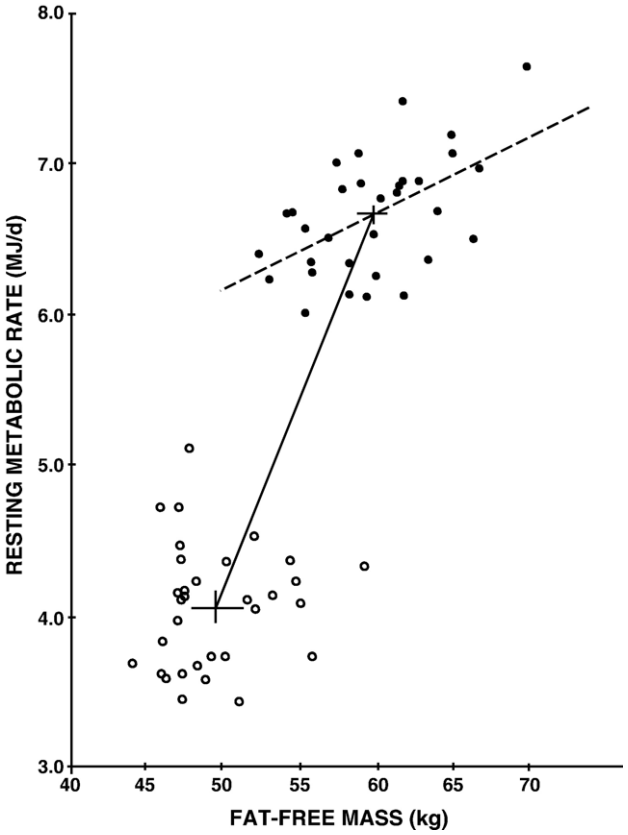

Fig. 1. Resting metabolic rate vs fat-free mass. The distribution represented by the solid black dots is the uncorrected data for the subjects of the Minnesota Experiment during the control period, and that represented by the open circles is the uncorrected data after 24 weeks of semistarvation. The solid line connects the centroids of the 2 distributions and has a slope of 263 kJ/kg per day, and the dashed line is a linear regression of the control data points with a slope of 51 kJ/kg per day.

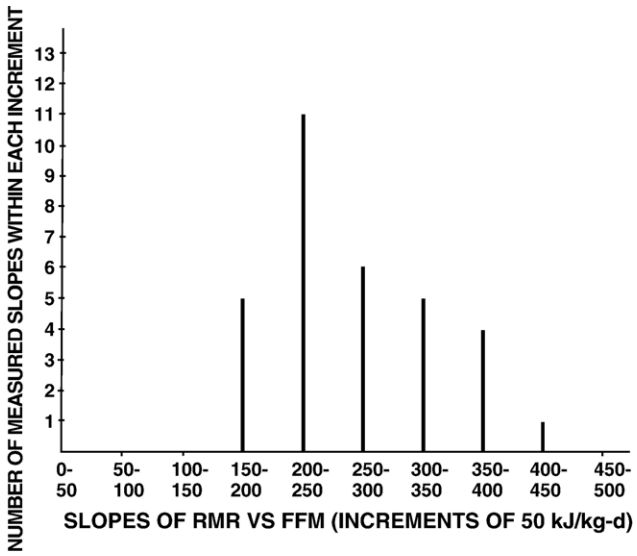

Fig. 2. A histogram of the individual slopes of connecting lines appropriate to the previous figure. The abscissa is divided into increments of 50 kJ/kg per day, and the ordinate gives the number of slope samples within each increment.

The ME provides information on the total body mass (TBM), the FM, and the rate of oxygen consumption for each of the 32 subjects. The FFM can be found by simple subtraction of the FM from the TBM, whereas the metabolic rate is found from the volumetric oxygen consumption rate by multiplication by the factor 20.3 kJ/L (see Appendix). The authors of the ME did not correct the FM results of individual subjects for excess fluid and bone mineral, but did make these corrections for the average group. This may have been the case because the methods introduced by Siri in 1961 [5] were not available in 1950 when the ME was published. We are able, however, to compare the differences of the group averages for the uncorrected and corrected FM at various times of the experimental period and find a maximal disagreement of 9.4%. We cannot say with certainty whether individual errors might be on the same order. We present the individual RMR vs FFM data in Fig. 1 keeping in mind that these data are uncorrected. Although errors in the FM may be on the order of 10%, the related fractional uncertainties in the FFM will be less because of the greater size of the FFM.

What is displayed in Fig. 1 is the distribution of the RMR vs FFM points for all of the subjects of the ME during the control period (solid circles) and after the semistarvation period of 24 weeks (open circles). A straight solid line is drawn between the centroids of the 2 distributions, which has the slope of 263 kJ/kg per day. A linear regression calculation is done on the control group alone and is found to have a slope of 51 kJ/kg per day, a correlation coefficient of 0.54, and is graphically displayed in Fig. 1 by a dashed line. Fig. 1 demonstrates the main thesis of this article that the longitudinal and cross-sectional dependencies of the RMR on FFM are significantly different. The linear regression study of the subjects of the ME before the

semistarvation period will be augmented by 9 additional works that include more diverse groups over larger ranges of both the RMR and FFM.

In Fig. 1, each of the 32 points of 1 distribution can be connected by a straight line to its corresponding point in the other distribution. Such a procedure results in a confusing diagram because of the different positions and slopes of the connecting lines. To avoid this confusion, a histogram of the distribution of slopes is constructed and is shown in Fig. 2, where the abscissa is arbitrarily chosen to have increments of 50 kJ/kg per day and the ordinate gives the number of RMR vs FFM slopes within each increment. Unexpectedly, the histogram is asymmetric, non-Gaussian, and resembles a binomial or Poissonian distribution, which suggests that the quantity plotted on the abscissa may be a discrete variate [6]. This finding may be significant on the biochemical molecular level. The least value of the slopes indicated in the histogram of Fig. 2 is 158 kJ/kg per day, and the greatest is 405 kJ/kg per day. The normalcy of these 2 limiting slope values is not judged in this article; however, the possibility exists that extreme values could result from physiological malfunction. Although a straight line is a useful graphical tool in connecting the points of Fig. 1, the question may be raised as to whether such straight lines have any physical reality. We argue here that the linear assumption is a reasonable one, although no firm experimental demonstration is yet evident for individual subjects. We will presently see that there is a group linear relation and display this in Fig. 3; however, the linear behavior of the group, although suggestive, does not strictly require the individual members of the group also to behave linearly. The argument that we present in support of individual linearity is based on 3 assumptions. The first assumption is that protein catabolysis is the main source of energy in the FFM. We will later justify this assumption by indicating that the total energy stored in glycogen is less than 4% that of the energy stored in protein. The second assumption is that all proteins of the body are structurally and chemically similar. If such is the case, the energy transferred out of the protein would have a constant ratio to the mass change of the protein. This is generally assumed to be true as is indicated by nutritionists assigning a single energy conversion factor for protein as well as other food types. The last assumption is that in each individual, the rates of the biochemical reactions involved in energy transfer from protein are determined by constant but different parameters maintained by each individual.

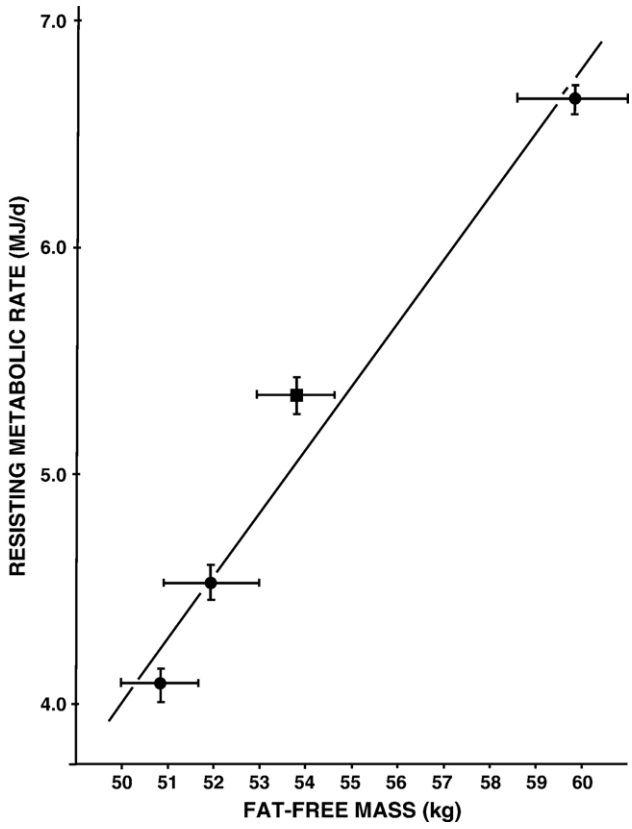

Fig. 3. Longitudinal RMR vs FFM. The 3 points indicated by circles were determined during the semistarvation period, and the single point indicated by a square was measured 12 weeks after the conclusion of semistarvation. The solid straight line results from least squares fit and has the slope of 280 ± 50 kJ/kg per day.

The assumptions made in the previous paragraph indicate that a linear RMR vs FFM curve is a reasonable possibility. One definition of a straight line is that it is a curve of fixed slope. We state this definition here as

$$\mathrm{d(RMR)/d(FFM)} = \mathrm{a} \tag{1}$$

where d is the differential operator, the symbol, a, is the fixed slope in units of kJ/kg per day, and the other symbols have already been defined. This simple differential equation is only rarely explicitly stated, but we do so here to remind the reader that the slope of Eq (1) is really a differential concept, that is, a limit of infinitesimal quantities. Because our assumptions of linearity are based on biochemical molecular changes, an infinitesimal approach is appropriate in dealing with the energy rate produced by the FFM. The solution to Eq (1) is

$$\mathrm{RMR} = \mathrm{a(FFM)} + \mathrm{b}, \tag{2}$$

where the constant of integration, b, is in units of kilojoules per day and is referred to as the offset term.

The ME gives tabulated mean corrected FMs, TBMs, and RMRs at 4 different times during and after the semistarvation period. This allows us to plot 4 distinct RMR vs FFM points that are displayed in Fig. 3. The error bars are calculated as SEMs. Three points in Fig. 3, indicated by round black dots, relate to the semistarvation period, whereas 1 point, indicated by a black square, was obtained 12 weeks after the conclusion of the semistarvation period. A least squares fit of the 4 points of Fig. 3 gives $a = 280 \pm 50$ kJ/kg per day and $b = -9994 \pm 2000$ kJ/d with a correlation coefficient for the fit of the already averaged points of 0.985. The given uncertainties are estimated by changing the slope of the least squares straight line and

judging the limitation of a reasonable fit. This technique leads to the estimation of the 2 correlated uncertainties.

Of the 4 points used in Fig. 3, the one taken 12 weeks after the end of semistarvation appears to be less collinear than the other 3 points and even suggests a curvature to the fit of all 4 points. The less than perfect linear fit in Fig. 3 is the main source of error in this article.

Because Eq (2) gives the metabolic energy rate, it must always be positive or zero. If we replace the RMR term in the equation with the zero value, we get

$$FFM_o = -b/a, \quad (3)$$

where we have used the subscript to remind us that the FFM of Eq (3) is that which does not contribute to the RMR and represents the mass of inactive tissue; this is our fundamental definition of inactive tissue mass. In the case of the ME, we calculate FFM_o = 35.7 ± 9.6 kg, which is 60% of the initial FFM. Conversely, the active tissue mass is 24.0 ± 9.6 kg or 40% of the initial FFM. Keys et al [1] cite Rubner [7] for creating the concept of active tissue in 1902. Rubner estimated this quantity to be 37.8 kg for a man of 60-kg mass. The average subject of the ME had an initial TBM of 69.7 kg. Keys et al [1] calculate the active tissue mass by subtraction of the FM, bone mineral mass, and thiocyanate space from the TBM and find an initial value of 39.9 kg, which is 67% of the initial FFM.

Webb [8], writing in 1981, states, "active tissue mass is a concept without a clear definition but is taken to be the sum of the masses of organs like brain, muscle, and liver which have high metabolic activity, and excludes those parts of the body mass which have low metabolic activity, like adipose tissue, bone, and skin." The definition of the active and inactive tissue mass used in this article follows from the extrapolation of the linear Eq (2) to zero value of the RMR and is independent of organ systems and their specific activity. The linearity suggested in Fig. 3 also implies that the elements of the active tissue mass all energetically behave similarly. This view is consistent with the idea that various organ systems are more active than others because they have a proportionally higher density of active tissue, but it does stress the similar energy reactions of all of the active elements of the body. If the reader perceives that the fit of Fig. 3 is not linear, then the idea that all active tissue elements behave similarly must be modified.

We now justify our assumption that the glycogen component of the active tissue mass is small. Best and Taylor [9] write that glycogen can be as much as 1% of the muscle mass and 15% of the liver mass. These authors state that the muscle mass is half of the TBM and the liver mass is 3% of the TBM. Using these statements without judgment, we calculate the glycogen mass to be 0.67 kg for the average subject of the ME. Keys et al [1] provide a table summarizing the work of Moulton [10], who measured the muscle and liver glycogen in both very fat and emaciated steers and reported his results in terms of the FFM. If we take Moulton's measurements for the very fat steers and apply them to the subjects of the ME at the beginning of semistarvation and the results for the emaciated steers applied at the end of semistarvation, we get respective values of the glycogen mass to be 0.81 and 0.71 kg. In this case, the beginning and final mass of glycogen does not change very much and, hence, the difference cannot contribute much to total energy balance. If we take the glycogen mass to be as much as 1 kg and compare this with the total active tissue mass of about 24.0 kg, the ratio is 0.04. Because protein and sugars have essentially the same Atwater factors, we conclude a worst-case scenario where protein accounts for 96% of the energy stored in the FFM, whereas glycogen accounts for 4%.

Kreitzman et al [11] did studies of 11 women put onto a restricted diet providing 25% of their maintenance energy requirements and found that a mean loss of glycogen of 400 g occurred after 4 days. The decrease in glycogen was accompanied by hydration losses that were 3 to 4 times the glycogen mass change. In the ME, the dietary restriction was less severe, being about 50% of the maintenance energy requirement, and was carried on for a much longer period. The energy density of change of the FFM in the ME was 8.56 ± 1.67 MJ/kg [4], which, if related to protein energy density, shows a hydration of about 50%. The point of this paragraph is that small amounts of glycogen with associated

Table 1
Cross-sectional data

Reference	*a* (kJ/kg per day)	*b* (kJ/d)	No. of subjects	Correlation coefficient	RMR for FFM = 59.70 kg (kJ/d)	Remarks
Keys et al [1]	51.1	3622	32	.55	6673	Basal, uncorrected
Webb [8]	70.5	2330	15	.93	6539	Sleeping
Ravussin et al [12]	87.1	1971	30	.82	7171	Resting
Ravussin et al [13]	73.3	2072	177	.83	6488	Sleeping
Ravussin et al [13]	87.5	2001	177	.82	7225	Basal
Owen [14]	98.8	779	104	–	6677	Resting, 95% confidence level of ± 1.76 MJ/d
de Boer et al [15]	66.0	2588	30	.88	6528	Sleeping
Rumpler et al [16]	70.7	2809	5	.98	7030	Basal
Leibel et al [17]	54.8	2805	41	.65	6077	Resting
Weyer et al [18]	86.1	1722	916	.80	6862	Sleeping, 500 Pima Indians

water of hydration do not appreciably alter the much larger change of protein that also carries with it water of hydration.

The ME provides limited cross-sectional data of the RMR vs FFM dependency. We have augmented this with 9 other works that are much more diverse in terms of sex, age, TBM, ethnicity, and sample size. The results for the 10 works are presented in Table 1 in terms of their linear regression formulations. In compiling the table, we have selected only those works that measured metabolic rates under the conditions of rest, sleep, or a basal state to avoid the thermal effects of exercise and food processing. In the work of Ravussin et al 13], the metabolic rates of both sleep and the basal state were measured with the results that sleep gives lower metabolic rates than does the basal state. Displayed in Table 1 is a column that represents the calculated metabolic rates for a value of 59.70 kg, which corresponds to the initial FFM of the subjects of the ME. Of the 10 tabulated works, basal and rest have 3 entries, and sleep has 4. We calculated the average results for each state and found that for sleep, the metabolic rate is 6604 ± 173 kJ/d; for the basal state it is 6976 ± 280 kJ/d; and for the rest it is 6642 ± 548 kJ/d, where the indicated uncertainties are SDs. The coefficients of variation in these 3 cases are 0.026, 0.040, and 0.083, respectively. Interestingly, this implies that the condition of sleep is the most reproducible for metabolic measurements, the basal state is less so, and the resting state is the least reproducible. The averaged metabolic rate for all 10 works for FFM = 59.70 kg is 6721 ± 352 kJ/d, which has a coefficient of variation of 0.056. Because the accuracy of this work is ultimately limited by the fit indicated in Fig. 3 that yields a 20% uncertainty, a quantity larger than all the preceding coefficients of variability, our earlier assumption that the condition of the metabolic state is not relevant to this work is justified. The RMR was measured to have a value of 6668 ± 67 kJ/d, which agrees with the averaged case for the 10 works in the table. If the results of the uncorrected ME are not included, the remaining average is calculated to be 6733 ± 373 kJ/d.

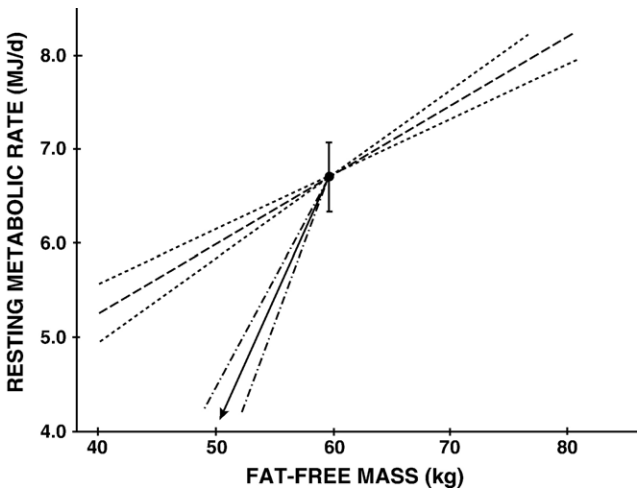

Fig. 4. Resting metabolic rate vs fat-free mass. The straight solid line with the arrowhead represents the longitudinal decrease of the RMR during semistarvation. The accompanying dotted-dashed lines are the associated uncertainty limits. The dashed line is the average cross-sectional behavior for the 10 research efforts reported in Table 1. The dotted lines are the associated uncertainty limits. The point from which all lines emanate is common to both data sets. The indicated error bar is the larger of the 2 uncertainties.

When the cross-sectional data of Table 1 are averaged to fit the form of Eq (2), we find a = 74.6 ± 15.2 kJ/kg per day and b = 2331 ± 783 kJ/d. The uncertainties quoted here are taken to be independent of each other.

In Fig. 4, we have graphically displayed the averaged results of the cross-sectional data of Table 1 starting from the initial FFM of the ME along with the longitudinal data. The solid line represents the longitudinal behavior of the subjects, and the dashed line is the averaged cross-sectional relation. The expected uncertainty for the longitudinal case is shown by 2 intersecting dotted-dashed lines emanating from the initial RMR point, whereas the 2 intersecting dotted lines represent the uncertainties in the cross-sectional data. The display in Fig. 4 is an attempt to show that the cross-sectional and longitudinal RMR dependencies are fundamentally different and are well outside the statistical uncertainties.

3. Conclusions and speculations

The main thesis of this article is demonstrated in Fig. 4 where the cross-sectional data for 10 separate studies are found to have a slope of 75 ± 15 kJ/kg per day, whereas the longitudinal data of a single study, the Minnesota Experiment, are found to have a slope of 280 ± 50 kJ/kg per day. In our theoretical formulation, we have used the 2-reservoir model to divide the body into the FM and the FFM. In addition, we deduce the FFM to be composed of active and inactive components. This latter idea allows us to consider the differences between longitudinal and cross-sectional data. We hypothesize that the decrease in active tissue alone in the longitudinal case is responsible for the large slope of the RMR vs FFM linear curve. The lesser slope of the cross-sectional data can be considered to occur from the admixture of active and inactive tissue that results from the change in size of different individuals. This structural allometric feature is viewed as a simple “dilution” problem. Thus, for different individuals who have the same longitudinal RMR vs FFM slope as the average subject of the ME and who also follow the average cross-sectional line of Fig. 4, we calculate that an increase of 1 kg of active tissue is accompanied by 2.70 kg of inactive tissue, or put in another way, the increase in active tissue is 27% of the change in the FFM. Keys et al [1] suggested that 4% of the initial TBM was bone mineral. In terms of the initial FFM, this would be 5%, and the aqueous component would be 55% with a large uncertainty. We should not confuse the initial inactive tissue fraction of the subjects of the ME, which was 60%, with the incremental fraction, which is about 73%. We will show that larger individuals should have a larger fraction of inactive tissue. A

possible identification of the active tissue is that it consists of protein, glycogen, and bonded water contained within the cellular structure. Inactive matter is mainly bone mineral and water. Some inactive water is contained within the extracellular space along with bone mineral but some, as we will deduce, is found within the cell itself. The difference between active and inactive water within the cell is presumed to be determined by the degree of bonding between the water and oxygen interactive cellular molecules. Active water is bonded and inactive water is not.

As indicated in the "Introduction," the offset term b for an individual is related to the cross-sectional behavior of the group. If we use a linear formulation for both the individual and the group, we can derive the relation

$$-\mathrm{b} = (\mathrm{a} - \mathrm{a}')(\mathrm{FFM}) - \mathrm{b}', \tag{4}$$

where the primed symbols refer to the group and the unprimed to the individual. The quantity $-b$ on the left of Eq (4) represents a positive quantity. Eq (4) holds for individuals who have similar longitudinal behavior and whose cross-sectional dependency is defined by the parameters a' and b'. Eq (4) shows that the offset term changes for individuals of different FFM. Another way to consider Eq (4) is to reformulate it so as to represent the fractional change of the inactive tissue for different individuals of increasing FFM. Such a reformulation yields the relation

$$\mathrm{FFM_o/FFM} = [(\mathrm{a}-\mathrm{a}')/\mathrm{a}] - [\mathrm{b}'/\mathrm{a}\ (\mathrm{FFM})]. \tag{5}$$

Using the values of the parameters that have already been evaluated, we rewrite Eq (5) numerically as

$$\mathrm{FFM_o/FFM} = 0.73 - 8.33/\mathrm{FFM}, \tag{6}$$

where the fraction of inactive tissue, $\mathrm{FFM_o/FFM}$, is dimensionless and the FFM is given in kilograms. Eq (6) is graphed in Fig. 5 and shows a monotonic increase of the fractional inactive tissue but at a decreasing rate. The reader should be aware that both Eq (6) and Fig. 5 apply to fully hydrated individuals. In the derivation of Eq (6), we have used values of a, b, and b' that have uncertainties that are not shown in Eq (6) or in Fig. 5 but that will be indicated in our derived results from Eq (6). The 2 interesting values that we can calculate from Eq (6) are the asymptotic value of the inactive tissue fraction and the FFM that corresponds to zero inactive tissue mass. The asymptotic value of the inactive tissue fraction is 0.73 ± 0.23. The large uncertainty in this value results from the combination of uncertainties in the parameters a and b. Webb and Abrams [19], using oxygen 18 isotope methods, measured the total fractional water of the FFM to be 0.72 ± 0.02. Although our result is very imprecise when compared with that of Webb and Abrams, the close agreement with our asymptotic inactive fraction suggests that as different individuals increase in FFM, the increase in their inactive fraction is likely aqueous in content. The other interesting calculation that we can perform is to determine the value of the FFM when the inactive tissue fraction is zero. We calculate this value to be 11.41 ± 4.75 kg. The large 42% uncertainty results from a combination of the uncertainties in the parameters a, b, and b'. Because this value contains no inactive tissue, it must all be active tissue mass. The value of the inactive tissue fraction must be between zero and one. For the active tissue mass to be less than 11.41 kg, the inactive tissue fraction becomes negative, which cannot be. This suggests that the lowest possible value of active tissue mass for the subjects of the ME is 11.41 kg, a possible criterion of mortality. At the end of the semistarvation period, the subjects had an active tissue mass of 14.17 kg.

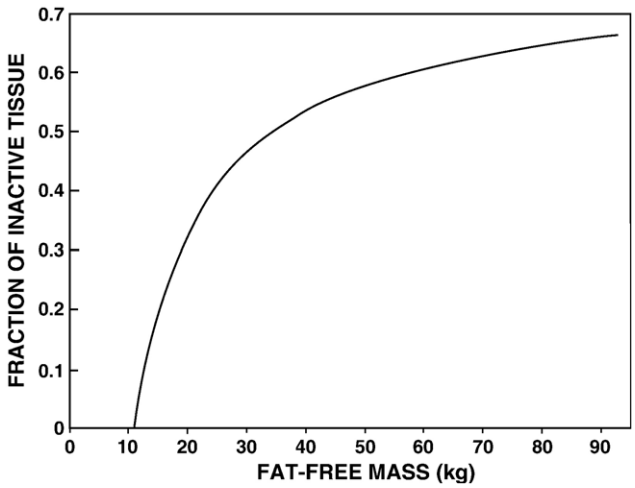

Fig. 5. The inactive tissue fraction of the FFM vs the FFM. Associated uncertainties appear in the text. The population of individuals represented by this graph is fully hydrated.

As we have pointed out, the cross-sectional dependence of the RMR on the FFM has been tabulated for 10 separate works, whereas the longitudinal dependence has been quantitatively demonstrated only for the single work of Keys et al [1]. In the next several paragraphs, we will cite experimental works that are consistent with the results of the ME and that indirectly support it.

Leibel and Hirsch [20] put 26 seriously obese patients on a ration of 2.51 MJ/d for an average period of 202 days and observed that their TBM fell from 152.5 ± 8.4 to 100.2 ± 5.7 kg and that their total energy expenditure (TEE) fell from 15.28 ± 0.75 to 9.09 ± 0.50 MJ/d. Leibel and Hirsch pointed out that the decrease in the TEE could not be explained by activity considerations alone. No measurement of the FFM was made in this work. We suggest that the large decrease in the TEE likely resulted from the subjects following the rule of Eqs. (1) and (2) where the slope a is similar in value to that of the ME leading to the large decrease in the RMR component of the TEE. An unexpected observation made by Leibel and Hirsch was that the reduced subjects had lesser values of their TEE than did their controls whose TBMs were smaller by about 40 kg. This is consistent with the idea that the active tissue mass of the subjects had rapidly decreased to values below that of their controls, whereas

their inactive tissue mass remained significantly greater than that of the control subjects. A mathematical analysis of an analog model of this case is presented by this author in the appendix of reference [4]. Leibel et al [17] have made measurements of the RMR vs FFM dependency for subjects losing 10% and 20% of their initial TBM, but this author was unable to extract quantitative information from their published graphical presentation.

Roza and Schizgal [21], using exchangeable potassium techniques, measured the body cell mass (BCM) for 168 men and 167 women. According to these authors, "the BCM is the total mass of metabolically active cells and is therefore that component of body composition which is responsible for oxygen consumption, CO_2 production, and the work performed by the body." This description of the BCM appears to be close to our understanding of the active tissue mass. We will shortly see, however, that there is a distinction to be made between the 2 concepts with the understanding that the BCM is likely to be the closest isolated biological system that can represent the active tissue mass. Roza and Schizgal do linear regression studies of the dependence of the resting energy expenditure (REE) as a function of the BCM and find a slope of 216 kJ/kg per day for men and 214 kJ/kg per day for women with respective correlation coefficients of 0.86 and 0.80. These values are to be compared with the equivalent quantity of 280 ± 50 kJ/kg per day, which we report as the longitudinal slope of the RMR vs FFM linear regression of the ME. It is our estimate of the Roza and Schizgal experiment that the quoted slopes have uncertainties of about ± 25 kJ/kg per day. The slopes determined by Roza and Schizgal do not agree with the cross-sectional value of 75 ± 15 kJ/kg per day, but almost agree with the longitudinal results of the ME. The reason why we feel that the BCM and active tissue mass are not quite the same concept is based on the experimental fact that the results of the linear regression studies of Roza and Schizgal do not pass through the REE-BCM origin. Roza and Schizgal find the value of the REE to be 716 kJ/d for men at a zero value of the BCM and an equivalent value of 1360 kJ/d for women. Our concept of active tissue mass results from the extrapolation of the RMR vs FFM linear regression to a point that defines zero active tissue mass. If we assume that the BCM contains mostly active tissue mass and some inactive tissue mass, we can use a "dilution" model as suggested earlier to determine that for men the BCM contains 77% active tissue and 23% inactive tissue. We will return to this point in our discussion of famine edema. In 1982, Doré et al [22] put 19 seriously obese metabolic ward women on a ration of 3.35 MJ/d for a period of 1 year during which the average TBM fell from 104.5 ± 2.1 to 73.7 ± 2.4 kg and the resting oxygen consumption decreased from 290.0 ± 7.5 to 234.0 ± 6.0 mL oxygen per minute. Using potassium 40 isotope techniques, Doré et al concluded that there was an average loss of 8.1 kg of lean tissue mass. From these data, we calculate that the slope of the RMR dependence on the lean tissue mass was 202 ± 57 kJ/kg per day. It is likely that Doré et al, using the potassium method, were actually measuring the BCM as was later identified by Roza and Schizgal [21] in 1984. The results of the 2 experiments with regard to the RMR dependence are in close agreement. The results of the Doré et al work do not agree with the cross-sectional data of Fig. 4 and also experimentally show that seriously obese patients lose FFM when subjected to a severe dietary restriction for a long time. This latter observation is consistent with the ideas that the FM has a limited energy-transfer ability [4], which when exceeded, causes the FFM and the RMR to decrease. It is possible that the decrease in the RMR follows a rule similar to that for the ME.

As indicated earlier in this article, the situation of famine edema must be considered. Keys et al [1] report that at the end of the 24-week semistarvation period, the experimental subjects had 6.25 L of excess fluid. Russell [23], in an article dealing with the social, psychological, and humanistic problems of the subjects of the ME, pointed out that the excess edematous fluid was particularly annoying for the subjects in terms of ill-fitting clothes and shoes. Earlier in this article, we deduced from the linearity of the RMR vs FFM curve of Fig. 3 that the inactive component of the FFM was a constant quantity. In an article by this author [4], the last 6 weeks of the semistarvation period led to a constant active component because of the equilibrium between the food energy input rate and the decreased RMR and activity expenditure of the ME subjects. Weyer et al [24] offer similar ideas about metabolic adaptation. Surprisingly, during the last 6 weeks of semistarvation when the starvation edema was at its worst, the FFM held to a constant value of 49.86 ± 0.06 kg [4], where the quoted 0.06-kg uncertainty is the SD of 6 weekly measurements. This constancy of the FFM implies that there was no net mass change in the last 6 weeks because of the free ingestion of external water during the semistarvation period and raises the question as to the source of excess edematous fluid. We suggest that the excess fluid is produced from within the inactive matter; that is, some of the inactive tissue mass that is not measurable by thiocyanate dilution is transformed into extracellular water, which is measurable by this technique. In our discussion of the Roza and Schizgal work [21], we calculated that 23% of the intercellular mass was inactive, presumably unbonded water. The total remaining 77% of the BCM was active tissue, which for the ME had an initial mass of 24.0 kg. A simple proportion shows that because 77% of the BCM is equivalent to 24.0 kg, then 23% is equivalent to 7.2 kg of inactive material, which includes a large compounded uncertainty of ± 5.0 kg. Thus, within the limits of the uncertainty, the inactive water initially within the BCM is sufficient to provide for the 6.25 L of edematous fluid appearing in the latter stages of semistarvation.

The advancement of the ideas presented in this article depend on accurate measurements relating the TBM and the FM. Traditionally, the FM has been determined by underwater weighing; however, with the appearance of closed-chamber pneumatic devices, more precise determination

of body volume and density leading to accurate values of the FM may become a much easier procedure.

There is an unexpected feature of this work that the author wishes to bring to the attention of the reader, namely, the slope of the longitudinal RMR dependence on the FFM has a value of 280 ± 50 kJ/kg per day, whereas the maximal rate of energy transferred out of the FM has a value of 290 ± 25 kJ/kg per day [4]. The near agreement of these 2 quantities possibly suggests the presence of an as yet unknown optimization principle. This author [25] has demonstrated that the rate of energy transfer from the FM is near optimal for maximizing the survival time of semistarved subjects. Briefly put, if the rate of energy transfer out of the FM were zero or very small, little survival benefit would accrue to the subject. This would be equivalent to the subject carrying around a useless load. It is not generally recognized that the FFM decays exponentially with a time constant of about 4 weeks if not supplied by an external energy source [4]. Thus, if the FM does not provide energy to the FFM, the survival time will be short. It is less evident that if the rate of energy transferred out of the FM were very large, this too would be detrimental to longevity. This case of a large or unlimited rate of energy transfer out of the FM corresponds to the popular concept that "the fat goes first." In the ME, the subjects were given a ration of 14.62 MJ/d during the control period and then cut back to 6.56 MJ/d. If the energy density of fat is 39.3 MJ/kg and if the initial FM was 9.66 kg, we can calculate that the FM would be exhausted in 47 days. If the condition of mortality is that which occurs when the active tissue mass falls to 11.4 kg, as was suggested to be a consequence of Eq (6), and we take the energy density of the active component of the FFM to be 8.56 MJ/kg [4], then we calculate that death would occur 13 days after the exhaustion of the FM for a total survival time of 60 days. The subjects of the ME survived for more than 168 days, and the popular model is demonstrated to be seriously incorrect. Because both a slow and fast transfer rate of energy out of the FM lead to a short longevity, an appropriate intermediate value will provide for a maximal survival time.

The point of the previous paragraph is to demonstrate the existence of an optimal value of one of the parameters, the energy rate of transfer out of the FM. There are, however, many other parameters included in the exact closed-form mathematical solution for the FFM in the energy-deficient mode derived and published by this author [4]. The longitudinal RMR is one of the important terms. It is possible that multiple parameter optimization techniques may lead to unknown and interesting relations between the variables. The mathematically inclined and interested reader is invited to consider this problem in detail.

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Appendix A

The accurate determination of the metabolic energy-production rate is commonly performed by respiratory exchange techniques along with measurement of urinary nitrogen; thus, in a given time, one must know the oxygen consumed, the carbon dioxide produced, and the change in urinary nitrogen. The production rate of carbon dioxide was not measured in the ME requiring that we rely only on oxygen-consumption data to determine the RMR.

Hughes and Goldman [26] have suggested the value, 20.3 kJ/L, as the conversion factor to be used in changing the volume of consumed oxygen into energy units for subjects on a mixed diet that we consider to be appropriate for the ME. Carpenter [27] presented a table of heat production for different oxygen rates based on a conversion factor of 20.2 kJ/L, which we presume was considered by that author to be a typical value for mixed diets. McLean and Tobin [28] use 1928 data of Lusk [29] and tabulate the results of 7 works that determine the produced energy by use of different calorific factors in the appropriate respiratory exchange equations. From these 7 results, we calculate the conversion factor to be (20.1 ± 0.3) kJ/L. We conclude that the use of the conversion factor 20.3 kJ/L is likely accurate to about 1% and is not a major source of error in the derived results of this work, which have errors in the 20% to 25% range.

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