Overnutrition and undernutrition as modifiers of metabolic processes in disease states

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ABSTRACT  Both overnutrition and undernutrition affect energy metabolism, with overnutrition raising energy expenditure and undernutrition lowering it. Fever is a powerful stimulator of thermogenesis. In diseases such as cancer, AIDS, diabetes mellitus, and rheumatoid arthritis, whether energy expenditure is increased or decreased often depends on how advanced the disorder is. Early on, when the greater protein turnover characteristic of these conditions is paramount, energy expenditure is increased. In addition, in diseases such as cancer, AIDS, and rheumatoid arthritis in which cytokines are released, the cytokines' thermogenic effect initially increases the metabolic rate. However, as the disease becomes more advanced and leads to cachexia, energy expenditure drops below normal. Acute conditions such as burns and trauma significantly raise energy expenditure, primarily by increasing sympathetic response and the release of catecholamines, which are powerful stimulators of energy expenditure.

KEY WORDS  Overnutrition, undernutrition, disease, metabolic rate, energy metabolism

INTRODUCTION

For this presentation, metabolism will be defined strictly as energy expenditure. The many other metabolic functions that occur in health and disease will not be discussed, as that would require a much more extensive review.

COMPONENTS OF ENERGY EXPENDITURE

In healthy persons, energy expenditure can be divided into 3 components: resting metabolic rate (RMR), which makes up most of the energy expenditure in sedentary individuals and generally accounts for 60–75% of total energy expenditure; the thermic effect of food, which represents 5–10% of 24-h energy expenditure; and physical activity, which represents 15–30% of total energy expenditure (1, 2) and can vary widely among individuals.

This paper will focus primarily on resting energy expenditure; of the 3 components, this is the one principally affected by overnutrition and undernutrition. Other contributors to this symposium will present data on thermogenesis as it relates to physical activity.

FACTORS AFFECTING ENERGY EXPENDITURE

Several factors affect human energy expenditure in both health and disease: age, sex, body size, hormones such as insulin and catecholamines, and nutritional status. Much of the difference between individuals, after the above factors are controlled for, is due to genetic variation. Research conducted by Bogardus et al (3), who work with Pima Indians in Arizona, illustrates the importance of genetics. These researchers measured the RMR of individual members of different families, calculated the average 24-h energy expenditure of these persons, and compared results by family. Individuals within families were much more likely to have similar RMRs than were individuals from different families (3). In addition, families varied in average energy output, with some families being low metabolizers and others high metabolizers. Thus, there was a clear familial pattern.

IF RMR is expressed in relation to fat-free mass (FFM) (ie, the metabolizing portion of the body), a straight line is found (1, 4). A regression equation can be derived for this relation (1). As individuals increase their weight, both their FFM and their energy expenditure increase. Similarly, as they lose weight, their FFM and energy expenditure decrease. At any given FFM, however, there is variation, with some persons having a higher energy expenditure than others. The biochemical or hormonal mechanisms responsible for these individual differences are not clear.

ENERGY EXPENDITURE

Shown in Figure 1 is a comparison of a prototypical 70-kg, nonobese person and a prototypical 105-kg, obese person. The lean person has 14 kg fat and the obese person has 40 kg. FFM is 56 kg in the first person and 64 kg in the second. The total weight difference between the 2 persons is 35 kg, whereas the difference in FFM is 9 kg. FFM expressed as protein (disregarding the water) is 11.5 kg in the nonobese person and 13.2 kg

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in the obese individual. Thus, individuals who are obese have not only increased fat mass but also increased FFM.

Because energy expenditure is related to the overall FFM of an individual, a group of obese persons will have both a higher total energy expenditure and a higher RMR than a group of lean persons who are matched for age, height, and sex (5). Within a group, however, energy expenditure will range widely, even when expressed as kg·kg\(^{-1}\)·d\(^{-1}\). This is true because, as mentioned previously, some persons are low metabolizers and some are high metabolizers. Average energy expenditure is 7–8 kJ/kg FFM, but there will be significant variations around these figures (3). Among Pima Indians in Arizona, Ravussin et al (5) studied individuals who were metabolically more efficient and expended less energy per day as well as those who had average or above-average energy expenditure. These individuals were followed for 4 y and the cumulative incidence of a 10-kg body weight gain was plotted for the 3 groups (those with low, middle, and high RMR). Predictably, those in the low-RMR group gained more weight over time than did persons in the other 2 groups (6).

Because the study by Ravussin et al is the only large, longitudinal, prospective study of an adult population to report such a finding, it needs to be duplicated in other population groups to ensure that it is a valid, predictable observation. Still, the study suggests that those individuals who have a low RMR relative to their FFM are at greater risk of gaining weight over the next decade than are those with higher RMRs.

**FORCES ACTING TO STABILIZE BODY COMPOSITION**

Certain forces in the body act to stabilize body composition. For example, if an individual who has a body mass index (in kg/m\(^2\)) of 25 loses weight, resting energy expenditure will decrease. One of the earliest and most famous reports of this phenomenon came from an experiment conducted at the University of Minnesota with conscientious objectors. The average weight of young men of normal weight who were given hypocaloric diets dropped from 67.0 to 59.8 kg (7); energy expenditure began to decline as soon as weight began to decrease. Other investigators reported a similar phenomenon with obese persons (8, 9). Thus, a reactive hypometabolic response occurs as soon as individuals begin to lose weight. This is a survival mechanism, a biological defense of body weight that limits the use of energy when energy is scarce. At the same time there is also a powerful drive to eat more, again in an effort to prevent weight loss. However, if food intake is controlled and persons are allowed to continue to lose weight, as occurred in the Minnesota study (7), energy balance remains negative because energy intake remains lower than energy expenditure, even though the body attempts to counteract this imbalance by decreasing energy expenditure further. Thus, any persons who are in an energy balance deficit will try to defend their weight by lowering their metabolic rate.

As shown in Table 1, in a group of men and women whose mean body weight was reduced from 98.2 to 79.8 kg (8), mean FFM dropped from 48.4 to 43.3 kg. Thus, the volunteers lost not only fat but also FFM. The change in their energy expenditure is shown in Table 2. Expressed in kJ/24 h, RMR dropped from 350 to 312.9. Expressed in terms of body weight, RMR increased from 3.56 to 3.92 kJ/kg, but in terms of kg FFM, the values at the beginning and the end of weight loss were exactly the same: 7.23 kJ/kg. Thus, the subjects dropped to an energy expenditure that was appropriate for their final FFM. They lost FFM, but maintained the same energy expenditure per unit of FFM. However, total RMR clearly dropped as they dropped their weight (8).

In a somewhat similar study conducted some years ago, Blair and Buskirk (10) observed a group of lean and obese women who were matched for age and height. They measured total energy expenditure, 24-h RMR, and nonresting energy expenditure over 24 h. The difference between the 2 groups was \(\approx 124.4\) kJ, of which 52.6 was RMR and \(\approx 71.8\) was nonresting energy expenditure. Thus, as weight is lost, not only RMR but also nonresting energy expenditure is decreased because significantly less mass is being moved around, requiring less effort to carry it (10–12).

The change in energy expenditure as one moves from a weight of 160% of ideal body weight to 100% of ideal body weight is \(\approx 120\) kJ/d (11, 12). This very large amount of energy saved per day has to be made up by decreasing food intake, increasing energy expenditure, or both to remain in energy balance after the weight loss.

**AGE AS A DETERMINANT OF ENERGY EXPENDITURE**

Age is an important variable in determining energy expenditure. If one plots the metabolic rate (expressed as kcal·m\(^{-2}\)·h\(^{-1}\)) in a group of persons in relation to age, it drops steeply in the first 20 y of life, flattens out somewhat to age 40, then flattens out even more but essentially continues to drop throughout the life span. In longitudinal studies, Keys et al (13) concluded that basal metabolism drops 1–2% per decade over the ages of

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**FIGURE 1.** Body composition of a prototypical lean man weighing 70 kg and of an obese man weighing 105 kg. FFM, fat-free mass.

**TABLE 1**

<table>
<thead>
<tr>
<th>Initial</th>
<th>Retest</th>
<th>kg (%)</th>
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</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>98.2 ± 23.8(^{\pm}) (100.0)</td>
<td>79.8 ± 18.6 (100.0)</td>
</tr>
<tr>
<td>Fat-free mass</td>
<td>48.4 ± 9.9 (49.2)</td>
<td>43.3 ± 8.1 (54.2)</td>
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\(^{1}\) Adapted from reference 8.

\(^{\pm}\) \(\pm SD.\)
20–75 y. Others have confirmed a reduction of energy expenditure with aging (14, 15). At age 75 y, men and women require a much lower daily energy intake to maintain their weight than they needed at age 20 y, even if they are as physically active at 75 y as they were at 20 y.

Part of the decrease in energy expenditure with aging is a result of decreasing body cell mass. Data from our body-composition laboratory show that, although there is a large scatter, the regression lines of body cell mass for age go down over time in both men and women (16). The actively metabolizing cell mass, which determines the amount of energy expenditure, decreases with aging, and thus resting energy expenditure goes down.

The difference in energy expenditure between men and women has a similar explanation. Women have lower RMRs than men not because of differences in sex hormones or other variables but because, for a given height, they have more fat and less lean body mass than do men.

DISEASE AS A DETERMINANT OF ENERGY EXPENDITURE

Diseases or medical conditions such as cancer, AIDS, diabetes mellitus, arthritis, and burns and trauma can increase energy expenditure. Furthermore, an elevated body temperature causes an increase in metabolic rate; for every increase in body temperature, energy expenditure increases. Whichever process is more prominent will determine whether energy expenditure is increased or decreased. Thus, cancer patients exhibit great variability in metabolic rate.

In an interesting study by Knox (19), the energy expenditures of 200 cancer patients and 200 normal patients were measured. In the normal patients, there was a close relation between the predicted metabolic rate and the observed metabolic rate (variation: ± 10–15%), but in the cancer patients, metabolic rates ranged from 50% to 175% of predicted, an extraordinarily wide scatter. Persons who are likely to be more hypermetabolic are likely to primarily show increased protein turnover changes, whereas those manifesting primarily cancer cachexia will likely have a drop in such turnover and be hypometabolic.

AIDS

As in the case of cancer patients, persons who develop full-blown AIDS can manifest either elevated or depressed metabolic rates. A recent study of the body composition in control, normal-weight persons without illness, who weighed an average of 77 kg, and in patients with active AIDS who weighed an average of 54 kg, sheds light on this question. Determinations of muscle mass by dual-energy X-ray absorptiometry, computed axial tomography, or neutron activation showed a significant difference between the AIDS patients and the control subjects; the AIDS patients had suffered a significant decrease in total skeletal muscle mass (20). Because energy expenditure is directly related to amount of FFM, a loss of muscle mass would be reflected in a lower RMR.

AIDS patients also manifest an increased turnover of leucine, which reflects an increased overall turnover of protein that leads to an increased metabolic rate. In a study by Macallan et al (21) comparing control, normal volunteers with a group of patients with active AIDS, in the fasted state the protein synthetic rate of the control group was 82.3 ± 4.2 μmol·kg⁻¹·h⁻¹, significantly lower than the comparable rate for the AIDS group of 111.6 ± 12.1 μmol·kg⁻¹·h⁻¹. In the fed state, the results were 113.0 ± 22.7 and 124.0 ± 11.5 μmol·kg⁻¹·h⁻¹ for the control subjects and the patients with active AIDS, respectively.

In another study, Grunfeld et al (22) compared a group of HIV-positive patients who did not yet have active disease with 2 groups of AIDS patients, 1 with active disease and 1 with secondary infection. The 2 groups with active disease had a higher energy expenditure than the control group. However, in some AIDS patients, this increased energy expenditure is more than counteracted by extreme cachexia, in which case the resting energy expenditure is below predicted, much as has been described for cancer patients (23).

Diabetes mellitus

Examinations of patients with diabetes mellitus have shown increased protein breakdown and synthesis. Indeed, patients with diabetes consistently have greater protein breakdown than do healthy individuals, as shown in Table 3 (24). Protein breakdown expressed as mg·kg⁻¹·h⁻¹ was 174.4 in lean healthy control subjects but 241.9 in diabetic patients. Protein synthesis was 144.9 and 180.5 mg·kg⁻¹·h⁻¹ in control subjects and diabetic patients, respectively, and there was a net protein loss of 31.7 mg·kg⁻¹·h⁻¹ in the control subjects compared with 61.3 mg·kg⁻¹·h⁻¹ in the diabetic patients (24). Thus, a very significant increase in protein turnover has been documented in diabetic patients, and this increase is greater the more that glucose homeostasis is out of control.

After insulin or sulfonylureas treatment and an improvement in glucose control, energy expenditure reverts toward normal (25, 26). The observed basal energy expenditure before and after insulin treatment are depicted in Table 4 (25). The basal energy

<p>| TABLE 2 |
|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th><strong>RMR</strong> (kJ/24 h)</th>
<th><strong>Initial</strong></th>
<th><strong>Retest</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>350.0 ± 74.2</td>
<td>312.9 ± 52.9</td>
</tr>
<tr>
<td>Per kg body wt</td>
<td>3.56 ± 0.67</td>
<td>3.92 ± 0.71</td>
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<tr>
<td>Per kg FFM</td>
<td>7.23 ± 1.29</td>
<td>7.23 ± 1.02</td>
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1 Significantly different from initial, P < 0.01.
importance of energy balance to the management of the disease process

The above discussion on overnutrition and undernutrition as modifiers of the metabolic process has underlined the importance of maintaining energy balance in managing disease. The increased energy expenditure that is manifest in these conditions causes a wastage of energy that is often difficult for the patient to counter. Although the natural defense of the body will be to lower energy expenditure as weight and body cell mass is lost, this will often not be enough compensatory change to stop an inexorable downward course of body mass. In strongly catabolic states, therefore, nutritional support, either parenteral or enteral, is mandatory.

the fat cell as an endocrine organ

Increasing evidence has been presented that the fat cell is an endocrine organ, secreting several active peptides into the circulation, including adipin, angiotensin II, leptin, and TNF-α (30). The peptide most publicized recently is leptin. In rodents, this hormone is low during cachexia and high during obesity. The evidence suggests that leptin is a signaling protein produced by adipose tissue that informs central regulatory processes about body fatness and helps to regulate body weight (31–34). In addition, it enhances thermogenesis and inhibits food intake (32, 33). Thus, circulating concentrations of leptin are important in regulating food intake and energy expenditure. Circulating plasma leptin concentrations correlate with body fat content (35–37); the adipose tissue signals the hypothalamus to increase or decrease energy expenditure according to the amount of fat mass in the body. A few cases have been described in which persons lacked the ability to make intact leptin or the leptin receptor, which has caused severe obesity (38, 39). In these patients, therapy with recombinant human leptin has caused very significant weight loss. Thus, there are human patients who manifest genetic lesions similar to those of the ob/ob mice, but they are very rare. Most obese persons have appropriately elevated leptin concentrations and may be called leptin “resistant” (34). Much more research is required to investigate the physiologic role of leptin in regulating food intake and energy expenditure.

future research

In numerous diseases, metabolic processes are affected so that either an increase or a decrease in energy expenditure occurs. Very little is known about the mechanisms by which these phenomena occur, however. Why is protein turnover increased in trauma and what signals turn on the response? How is metabolism slowed when weight is lost and what are the mechanisms involved? How does infection affect the production of energy? What characteristics of patients make some more susceptible than others to changes? What is the role of the various “uncoupling” proteins in enhancing energy expenditure? How are these uncoupling proteins regulated? Further investigation of these important processes is necessary.

TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Protein breakdown</th>
<th>Protein synthesis</th>
<th>Net protein loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg·kg·LBM$^{-1}$·h$^{-1}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>241.9 ± 26.1</td>
<td>180.5 ± 21.3</td>
<td>61.3 ± 6.8</td>
</tr>
<tr>
<td>Obese</td>
<td>206.6 ± 13.0</td>
<td>168.1 ± 12.4</td>
<td>38.5 ± 3.4</td>
</tr>
<tr>
<td>Lean</td>
<td>174.4 ± 14.1</td>
<td>144.9 ± 12.4</td>
<td>31.7 ± 8.1</td>
</tr>
</tbody>
</table>

$^a±SD. LBM, lean body mass. From reference 24.

TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Observed basal energy expenditure</th>
<th>Plasma glucose</th>
<th>β-Hydroxy butyrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kJ/24 h</td>
<td>mg/dL (mmol/L)</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Before</td>
<td>488.5 ± 14.4</td>
<td>347 ± 19 (19.3 ± 1.1)</td>
<td>3.34 ± 0.76</td>
</tr>
<tr>
<td>After</td>
<td>413.4 ± 11.7</td>
<td>104 ± 14 (5.8 ± 0.8)</td>
<td>0.08 ± 0.01</td>
</tr>
</tbody>
</table>

$^a±SEM. Adapted from reference 25.
REFERENCES


