



Analysis of energy metabolism in humans: A review of methodologies

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ABSTRACT

Background: Obesity is a consequence of chronic energy imbalance. We need accurate and precise measurements of energy intake and expenditure, as well as the related behaviors, to fully understand how energy homeostasis is regulated in order to develop interventions and evaluate their effectiveness to combat the global obesity epidemic.

Scope of review: We provide an in-depth review of the methodologies currently used to measure energy intake and expenditure in humans, including their principles, advantages, and limitations in the clinical research setting. The aim is to provide researchers with a comprehensive guide to conduct obesity research of the highest possible quality.

Major conclusions: An array of methodologies is available to measure various aspects of energy metabolism and none is perfect under all circumstances. The choice of methods should be specific to particular research questions with practicality and quality of data the priorities for consideration. A combination of complementary measurements may be preferable. There is an imperative need to develop new methodologies to improve the accuracy and precision of energy intake assessments.

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Keywords Energy expenditure; Dietary assessment; Clinical study methodology

1. INTRODUCTION

Obesity is an escalating global epidemic with considerable personal and societal consequences. In 2014, the World Health Organization estimated that more than 1.9 billion adults (or 39% of the world population aged 18 years and over) are overweight and among those over 600 million are obese [1]. As a major risk factor for a range of chronic diseases including diabetes, cardiovascular diseases and certain cancers, overweight, and obesity have been attributed to cause 3.4 million deaths in 2010 [2]. Obesity also imposes substantial economic impacts. In addition to a ~40% higher per capita medical spending than individuals with a healthy body weight [3], obesity also incurs indirect costs due to reduced workforce productivity, e.g. unable to work at full capacity, absent from work or premature mortality [4]. In the United States, it has been estimated that the national cost of obesity-related absenteeism ranges from \$3 billion to \$6 billion annually [5]. Despite the effort to create a supportive environment for healthy lifestyle and implementing aggressive interventions, there have been no indication for any declining trend to lessen the obesity epidemic [6].

Obesity, as a disease of excessive fat deposition, is essentially a consequence of chronic energy imbalance with energy intake consistently exceeding expenditure, which then leads to the storage of surplus energy in the white adipose tissue. While the solution to obesity appears to be as simple as reducing calorie intake (e.g. avoid energy-

dense food) and increasing energy expenditure (e.g. increase physical activity), the failure of decades of public health initiatives to remove the “obesogenic” environmental factors clearly indicates that obesity is a problem far more complex than the prevailing wisdom of “low will-power”. Indeed, we are yet to fully understand the sophisticated interactions between genetics, physiology, and cognitive behavior that regulate energy homeostasis. One of the greatest challenges in obesity research is to accurately measure energy intake and expenditure, as well as the related behaviors. Such measurement tools would allow for identification of causal associations between energy homeostasis and health outcomes, inform on the mechanisms by which energy metabolism is regulated, and accurately define how energy balance changes in response to interventions. In this article, we provide an in-depth review of the methodologies used to measure energy intake and expenditure in humans, with the aim of providing researchers with a comprehensive guide to conduct obesity research of the highest possible quality.

2. A BRIEF OVERVIEW ON ENERGY HOMEOSTASIS

2.1. Energy balance

Energy balance is the difference between energy intake and energy expenditure. Energy equilibrium, i.e., zero energy balance, is reached when metabolizable energy consumption matches perfectly with the amount of energy spent. A non-zero energy balance, on the other

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Received August 15, 2016 • Accepted September 12, 2016 • Available online 20 September 2016

<http://dx.doi.org/10.1016/j.molmet.2016.09.005>

hand, must implicate an equal change in the energy content of the body in the form of changes in the weight of some body constituent [7] which subsequently alters energy expenditure. In the case of a positive energy balance, basal metabolic rate increases with weight gain because of the growth of lean mass to support the expended fat depots, and, conversely, a decrease in basal metabolic rate when a negative energy balance triggers a reduction in body mass. Assuming energy intake remains unchanged after the initial intervention, one might expect that energy expenditure will eventually match energy intake and body weight will be stabilized at a new set-point.

In reality, however, when there is persistent deviation from energy equilibrium, changes in energy expenditure is no longer predictable on the basis of metabolic mass. Our CALERIE study [8], among many others [9,10], has shown that weight loss is associated with a reduction in 24-h energy expenditure up to 15% lower than what is predicted after adjustment for changes in body composition, whereas the opposite is observed in overfeeding [9,11]. A recent study on morbidly obese individuals reported a lower resting metabolic rate immediately following intensive diet and exercise interventions, which continued to decline (from -275 to -499 kcal/d) at 6 years post-intervention despite significant regain of both lean and fat mass [12]. These data clearly suggest a disproportionate change in energy expenditure not only during, but also well beyond, the dynamic phase of weight change, a phenomenon known as metabolic adaptation or adaptive thermogenesis. The relationship between energy balance and metabolic adaptation is illustrated in Figure 1.

Besides the changes in energy expenditure related to the changes in fat-free and fat mass, another obvious factor for changes in 24-h energy expenditure is of course an altered energy cost of physical activity given a different body mass. Variations in food intake also modify the amount of energy spent on nutrient processing and assimilation (thermic effect of food; see Section 2.3 below). It is perhaps somewhat intriguing that basal metabolic rate also has been shown to be disproportionally regulated relative to metabolic mass [13,14]. Some hypothesize a change in the fat-free mass composition. While this is supported by data from Bosy-Westphal and colleagues

[15] that demonstrated a small and yet significant greater loss of organ mass with high metabolic activity (e.g. heart, liver and kidneys) as compared to the total loss of fat-free mass following weight reduction. In recent years, there is emerging evidence for a link between mitochondrial dynamics, nutrient availability, and energy expenditure, which implicates some form of cellular bioenergetics adaptation. Mitochondria in cells under starvation have been shown to increase the ratio of ATP produced per unit of nutrient consumption, whereas those in nutrient excess increase energy waste in the form of heat via mitochondrial proton leak (for details refer to a recent review by Liesa and Shirihai [16]). In other words, we adapt to changes in energy supply and demand by adjusting our capacity and/or efficiency of ATP synthesis. Prolonged changes in mitochondrial dynamics (e.g. chronic positive energy balance in obesity), however, may lead to mitochondrial dysfunction characteristic of metabolic diseases [17,18].

2.2. Food intake

The regulation of food intake is primarily a feedback system that responds to both physiological (internal) and environmental (external) signals. These signals act directly on the brain or alter secretions from other organs, influencing ingestive behavior from meal size to diet selection, and impacting daily energy consumption. The majority of physiological signals come from organs that are involved in the acquisition and storage of nutrients (such as liver, adipose and skeletal muscle tissues), which inform on nutrient availability. Modulation of food intake occurs even before feeding begins. Sensory cues (taste, smell, texture and sight) and the thought or discussion of food are cephalic signals that trigger physiological response in preparation for a meal, which include increasing salivation and the secretion of gastric acid, orexigenic hormones, and insulin [19,20]. Upon ingestion, gastric distension stimulates the vagal mechanosensitive fibers that contribute to postprandial satiety [21]. The direct contact of nutrients with the gastrointestinal tract also stimulates the secretion of satiation hormones, mainly cholecystokinin, peptide YY, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1). Collectively these hormones activate the proopiomelanocortin/cocaine-

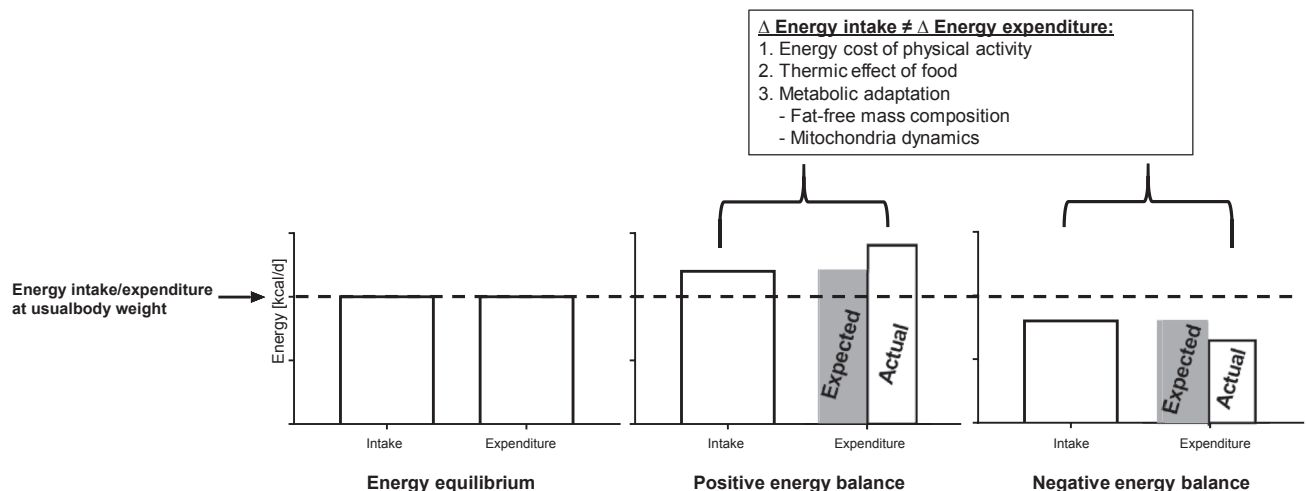


Figure 1: Illustration of energy balance and metabolic adaptation. When energy intake equals to total energy expenditure, a state of energy equilibrium is reached, and the body weight stays at the usual set-point. When energy intake exceeds or falls below the level required to maintain the usual body weight, energy expenditure no longer matches the intake (indicated by the gray shaded area), with expenditure exceeding intake in positive energy balance and the reverse for negative energy balance. Most of this difference is explained by changes in energy cost of physical activity associated with a different body mass and thermic effect of food. Metabolic adaptation refers to the phenomenon in which energy expenditure is adjusted independent of metabolic mass, possibly via altered mitochondrial dynamics, as a potential mechanism to restore body weight to the usual set-point.

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