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REVIEW

Insights into energy balance from doubly labeled water

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Obesity is defined as the excess storage of energy in the form of fat that results from imbalances between energy intake and expenditure. The study of the components of energy balance has undergone a significant advancement with the application of the doubly labeled water (DLW) method to the measurement of human energy expenditure. This manuscript includes a selective review of the studies that have utilized the doubly labeled method as it applies to the study of human obesity. Although generally now accepted, one of the major surprises from the early applications of DLW was that obese individuals have higher energy expenditures than lean controls. Moreover, weight gain, even in the already obese, is associated with an increase in energy expenditure as weight is one of the strongest predictors of total energy expenditure. Similarly, studies of weight loss treatment show a decrease in energy expenditure due to weight loss and due to adaptive changes in energetic efficiency, but these changes do not account for the common cessation of weight loss observed after 12–26 weeks of restriction. The accumulating data from the application of the DLW method suggest a need to place greater emphasis on mechanisms that lead to a mismatch between energy intake and expenditure rather than a continuing emphasis on energy intake or energy expenditure alone.
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Introduction

Energy can be neither created nor destroyed. Thus, the change in metabolically usable body stores is the difference between energy intake and energy expenditure, where energy intake is the metabolizable energy from the diet, and energy expenditure is the totality of all energy released as heat.[1] This is a simple equation, but its simplicity can lead one to oversimplify human energy regulation.

On the basis of national survey data, it is estimated that the average US adult gains about 0.5 kg over the course of the average year.[2] After a decade, a slow gain that is above or below average can be the difference between remaining at a healthy weight or becoming overweight or obese. Applying the energy balance equation and assuming that each pound of gain is 80% fat, a 0.5–1 kg annual gain represents a mere 10–20 kcal day^{-1} of excess energy intake of deficient energy expenditure. Given these small values, it appears simple to reverse that slow weight gain by instituting small changes in behavior.

The first limitation of the energy balance equation, however, has been that none of the terms have been easy to measure with accuracy under anything short of metabolic ward conditions. In the metabolic ward, one can measure the resting metabolic rate, the thermic effect of meals and the energy costs of specific physical activities using respiratory exchange analysis with precisions of a few percentage points.[3] Energy intake can be measured with similar precision using carefully weighed foods coupled with bomb calorimetry of both the food and the metabolic wastes.[3] Change in body energy stores can be measured by changes in weight and body composition, but this too has limited precision in terms of energy stored per day unless the time between measurements is several months or longer. Even these ideal measures, however, are subject to random errors that are 30 kcal day^{-1} or more. When the conditions are less ideal, such as those encountered outside of the metabolic ward, measurements have been more difficult and far less accurate and precise. Earlier to 1980, the more difficult term to measure was energy expenditure; resting metabolic rate could still be measured by bringing patients to an outpatient facility, but moderately long-term measures of total energy expenditure under free-living conditions were not possible.

This began to change when Nathan Lifson imagineered the doubly labeled water (DLW) method,[4] and his work was amplified when I stumbled across his work and applied the method in humans 25 years ago.[5] The method is based on the observation that the biological elimination rates of labeled hydrogen and labeled oxygen in water are different

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(Figure 1).[6] The hydrogen label in body water is diluted by water entering the body from beverages, food moisture, metabolic water and absorbed moisture; and water eliminated from the body in urine, water vapor and other efflux routes. Oxygen undergoes the same dilution and efflux but is also diluted by oxygen entering the body's metabolic pools as bicarbonate, because the oxygens in water and bicarbonate are in rapid isotopic equilibrium. The elimination of labeled oxygen from the body is therefore faster than that of labeled hydrogen and the difference between the two elimination rates is a measure of carbon dioxide production and thus energy expenditure. The vital practical aspect of the DLW method is that it is not necessary to collect the labeled carbon dioxide, but instead, it is only necessary to collect spot urines at the start and end of the metabolic period to calculate the isotope dilution spaces and elimination rates to assess energy expenditure. Between those two time points, usually a period of 1–2 weeks, the patient is able to engage in typical activities without restriction, and thus measurements can be made in free-living individuals.[6] The attributes of Lifson's work were soon recognized by animal ecologists, and the DLW method was commonly used for the study of small animals,[7] but it was not until 1982 that DLW was first validated in humans.[5] Others followed suit and the first formal meeting on the use of the DLW method was organized by Prentice *et al.*,[8] leading to the publication of a users manual that standardized a number of practices for the use of DLW method.

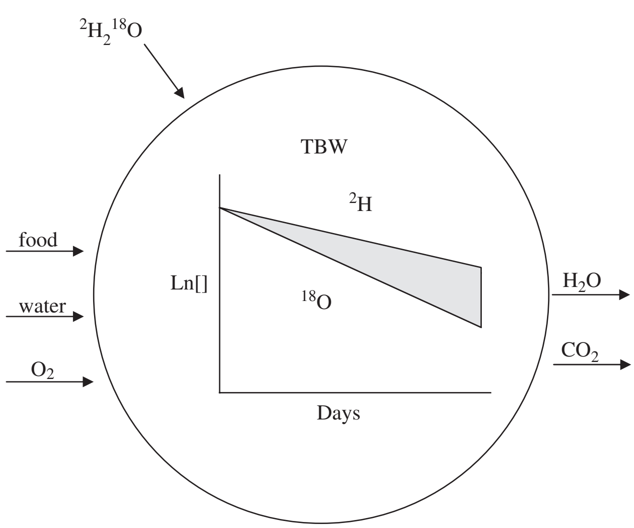

Figure 1 The stable isotope elimination rates of ^2H and ^{18}O from body water follow steady-state, single-compartment kinetics. Thus, the rate of water output $(rH_2O) = N_d k_d$ and the sum of the rates of water and twice the rate of CO_2 production $(rCO_2) = N_o k_o$, where N_d and N_o are the isotope dilution spaces and k_d and k_o are the isotope elimination rates. Combining these equations and solving for $rCO_2 = \frac{1}{2}(N_o k_o - N_d k_d)$. Energy expenditure can be calculated from the rate of CO_2 production and an estimate of the respiratory exchange ratio using standard indirect calorimetric equations. Accuracy of the calculation of CO_2 production requires a modification for isotope fractionation. Adapted from Lifson.[6]

It was not long after the first validations that the method was applied to study of human energy metabolism and obesity. Prentice *et al.*[9] compared the energy expenditures of lean and obese women and reported that, contrary to one of the major theories of the time, the obese had high levels of energy expenditure compared with the lean. This observation of greater energy expenditures in the obese was also reported by Bandini *et al.*[10] in adolescents, an age group still actively growing. As more data became available, it became quite evident that the energy expenditures of obese individuals generally increased with body size and that the increase was linear with weight or fat-free mass.[11] Even those with severe obesity have been reported to have higher rates of energy expenditure that are related to their even greater body size.[12] This relationship with body size was fully recognized in 2002, when the Macronutrient Committee in the process of generating the Dietary Reference Intakes under the auspices of the Institute of Medicine evaluated DLW measured total energy expenditures from a large number of studies and generated energy expenditure prediction equations based on weight, height and age.[13] Thus, the preponderance of data from DLW has not supported the hypothesis that obesity is associated with a low energy expenditure.

An exception to the above statement was the finding that low energy expenditure measured by DLW did indeed predict excess weight gain in a small study of 3-month-old infants born to obese mothers.[14] It was also noted during a follow-up analysis that these same children who became overweight during the 9-month follow-up also had increased energy intake.[15] A replication study was performed by Stunkard *et al.*[16] but in a larger group of children who were also selected on the basis of being born to obese or lean mothers and hence at high or low risk of excess weight gain. This study did not find confirming evidence of low energy expenditure at 3 months of age predicting excess weight gain but did confirm that weight gain was associated with energy intake and other correlates of energy intake during a test meal.[16] After additional years of follow-up with periodic measures of energy expenditure and test meal food consumption, it was found that the children born to obese mothers did gain more weight than those born of lean mothers, but that the relationship between energy expenditure and weight gain was a positive association, that is, the higher the energy expenditure, the greater the gain, and energy intake was the strongest predictor of weight gain.[17] A longitudinal study performed in preschool children also found a positive association between weight and energy expenditure and thus an absence of evidence of low energy expenditure leading to excess weight gain.[18] In contrast, a 2-year study of 9- to 11-year-old children did find a negative association in energy expenditure with the change in percent fat was reported, but when Tanner stage, gender and race were entered into the model, the relationship with energy expenditure weakened and only remained significant among African-American girls, indicating the possibility of confounding by more rapid Tanner staging in heavier individuals.[19] Finally, a longitudinal study in adult African and African-American women has also found a positive, rather than negative, association between DLW measured energy expenditure and subsequent weight gain.[20] Thus, the preponderance of data from longitudinal natural weight gain studies have not provided evidence of a low energy expenditure leading to weight gain.

The single consistent exception to the general finding that weight gain is not associated with a low energy expenditure has been the finding that weight regain in reduced obese patients is fastest in those with lower energy expenditures. Two longitudinal studies among women who had recently lost weight resulting in their no longer being obese found that low energy expenditure, particularly low levels of physical activity, were strong predictors of weight gain.[21,22] Two potential explanations for the finding that energy expenditure is negatively associated with weight regain in previously obese women, but not individuals who had not recently lost weight, is that the recent weight loss may predispose individuals to the influence of a sedentary lifestyle on weight gain more so than those who have not recently lost weight, or that the decreased energy requirement of a smaller body after weight loss may have to be coupled with a need to increase physical activity to cancel the difference between the energy requirement from before to after weight loss.[23]

The lower absolute energy expenditure among the previously obese who have lost weight is related to another hypothesis that had been difficult to address before the application of DLW to human studies, for example, that weight loss is associated with adaptive decreases in energy expenditure during active weight loss and that these changes are sufficient to account for the frequently observed plateauing of weight loss in the obese after 12–26 weeks of an energy restriction treatment.[24] This phenomenon was clearly documented in the Minnesota semi-starvation study of nonobese men who lost about 25% of their initial body weight under conditions of strict diet control and were found to have a nearly 50% reduction in resting metabolic rate.[25] The decreases in energy expenditure observed after restriction to similar energy intakes (roughly 1500 kcal day^{-1}) in obese individuals, however, while biologically significant, have not been found to be sufficient to reach energy balance on the energy-restricted diet.[26,27] The decreases in energy expenditure during energy restriction are relatively consistent between studies, but are too small to explain the slowing of weight loss and plateau effect usually observed after 12–26 weeks of energy restriction for the treatment of obesity.[28] The implication of these data is that there was noncompliance to the energy restriction prescription during the active period of weight loss in outpatient studies[29,30] that is not evident from self-reported energy intake due to under-reporting and that this under-reporting may worsen with time.[28] Indeed, by calculating energy intake from total energy expenditure and change in body energy stores, the average energy intake in excess of prescribed is often comparable to or larger than the energy restriction related decrease in energy expenditure.[29,30] Moreover, it has been shown that as the reduced obese begin to regain weight, their energy expenditure generally increases with the weight increase, again showing the positive effect of body size on energy expenditure.[31]

This observation that energy expenditure increases with body size has a major implication with regard to human obesity. It implies that the typical adult either gains weight by an increase in energy intake to produce a positive energy balance and storage of the surplus energy in the form of body tissue followed by a now higher habitual energy intake to support the larger body mass; or by a temporary reduction in energy expenditure producing a positive energy balance followed by an increase in energy expenditure and energy intake to the levels associated with the now larger body mass. Assuming that the natural history of weight accumulation in adulthood follows the pattern of holiday weight gain documented by Yanovski *et al.*,[32] the former appears to be the more likely mechanism, but short periods of inactivity have also been shown to lead to fat gain and thus the latter mechanism for an annual modest weight gain is also possible.[33] The latter mechanism, however, also requires that at the end of the periodic sedentary period that the individual must increase energy intake to sustain the high energy expenditure associated with the increased weight. In either event, weight gain is associated with a higher energy expenditure than before the weight gain.

This observation of increasing energy expenditures with body size was recently emphasized in a dramatic refinement of the calculation of the energy costs of weight gain in children, which included not only the cost of energy storage, but also the cost of a higher energy requirement.[34] These observations, however, lead to an apparent conundrum. Because energy can be neither created nor destroyed, obesity must result from a positive energy balance; yet weight gain increases energy expenditure, but this increased expenditure does not generally result in a return to energy balance and a halt to the slow increase in body weight. Thus, it is apparent that the mechanism underlying this annual weight gain for most individuals does not generally lie in a low energy expenditure in the face of an average energy intake, nor a high energy intake in the face of an average energy expenditure, but rather a continued imbalance between energy intake and expenditure. These differences, as discussed, are very small when presented on an average daily basis. Before weight gain, the energy intake and expenditure can be quite average but after the accumulation of excess fat to the point of obesity, both energy intake and expenditure will be higher than ‘normal’. The subsequent weight gain for both the nonobese and obese individual, however, is by definition a mismatch between the two. Thus, the knowledge gained when energy expenditure is studied alone or energy intake is studied alone is modest, and a better understanding of the causes of obesity lies in studying the factors that determine the mismatch between the two.[35] Fortunately, we can measure that gap in energy balance from longitudinal measures of weight and body composition with greater accuracy and precision that we can measure either energy intake or expenditure.

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Conflict of interest

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