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Assessment of energy expenditure: are calories measured differently for different diets?

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Abstract

Purpose of review—The prevalence and burden of obesity has reached alarming levels. The assessment of human energy expenditure enables the identification of obesity-prone and obesity-resistant individuals and helps to explain the short and long-term success of weight loss treatments. In this review, we describe the state-of-the-art methods used in the assessment of human energy expenditure and the impact of dietary intake on the interpretation of the data.

Recent findings—The reference techniques to assess energy expenditure in humans have not significantly changed during the last century. Today, indirect calorimetry, either using a metabolic chamber or a metabolic cart, is the favored method to assess human energy expenditure and is the only method enabling the assessment of macronutrient oxidation. The doubly labeled water method however provides accurate assessment of human energy expenditure under free living conditions.

Summary—Although energy expenditure and macronutrient oxidation can be assessed by simple calculations from oxygen consumption and carbon dioxide production, these calculations can provide erroneous results or require corrections and/or more complex interpretation when several biochemical pathways are simultaneously engaged. Such physiological mechanisms are often elicited by dietary interventions including, among other, gluconeogenesis, lipogenesis, ketogenesis, alcohol oxidation and under or overfeeding.

Keywords

doubly labeled water; energy balance; indirect calorimetry; nutrient oxidation; substrate balance

INTRODUCTION

The prevalence of obesity has increased worldwide during the past few decades [1,2], making obesity one of the largest public health burdens [3,4]. Obesity is the result of complex interactions between individuals' genetic background, environmental, behavioral and socioeconomic factors (Fig. 1) [4]. However, regardless of its cause, obesity is produced

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Conflicts of interest

There are no conflicts of interest.

by a sustained positive energy balance, that is energy intake exceeding energy expenditure. In normal circumstances, energy balance is tightly regulated and many biological processes maintain weight stability over time by matching energy intake to energy expenditure [4]. However, when exposed to the modern obesogenic environment, a large part of the human population presents a biological predisposition to excessive weight gain [5].

Over the past few decades, the assessment of energy expenditure has enabled the identification of several factors underlying the biological predisposition to excessive weight gain occurring in many individuals [4,6]. For instance, we were the first to describe that a low relative energy expenditure (adjusted for fat-free mass, fat mass, age and sex) is a risk factor for body weight gain. More recently, changes in energy expenditure in response to acute perturbations in energy intake (e.g. 24-h fasting or 24-h of 200% overfeeding) have been shown to be predictive of weight gain [6-8]. Nowadays, the presence of biologically determined thrifty (prone to weight gain) or spendthrift (resistant to weight gain) phenotypes is recognized [8]. Such thrifty and spendthrift phenotypes also predict the individual response to weight loss treatment [9]. Even more importantly, a reduction in energy expenditure larger than expected by changes in body weight and composition (metabolic adaption) is triggered in response to weight loss and is partially responsible for weight regain [10]. In summary, alterations of energy expenditure determine the propensity of many individuals to become obese and seem to cause a resistance to weight loss and a propensity to regain the weight after a weight loss intervention.

The maintenance of energy balance requires the maintenance of the balance of the three major macronutrients, that is fat, protein and carbohydrate (Fig. 2). In contrast to dietary carbohydrates, protein and alcohol, increased dietary fat intake does not induce rapid increases in fat oxidation thus causing body fat accretion. Moreover, the interindividual variability in the capacity to adjust substrate oxidation to substrate availability (i.e. metabolic flexibility) is hypothesized to be a determinant of ectopic fat accumulation and insulin resistance [11,12]. Together, the above observation highlights the importance of assessing not only total energy expenditure, but the contribution of different macronutrient oxidation rates to energy expenditure.

Below we describe the state-of-the-art methods to assess human energy expenditure and substrate oxidation, and the impact of dietary intake on the interpretation of the data.

METHODS TO ASSESS HUMAN ENERGY EXPENDITURE

The reference techniques to assess energy expenditure in humans have not much changed during the last century. The most accurate methods are direct calorimetry and indirect calorimetry, which both require the individual to be confined in small rooms (Table 1). Therefore, many methods for assessing energy expenditure in free-living conditions have been developed including heart rate (HR) monitors, accelerometry and the doubly labeled water (DLW) method.

Direct calorimetry

As mandated by the first law of thermodynamics, all energy used by the human body will eventually be dissipated as heat, except for the energy used to perform mechanical work [15]. Thus, in conditions of thermal balance, energy expenditure can be accurately assessed by measuring heat production. Direct calorimetry has been used to assess human energy expenditure since the 18th century. Direct calorimeters are small, insulated chambers in which heat released by the person is measured. Due to the high cost of building and maintaining the required equipment as well as some limitations, such as the inability to adequately assess energy expenditure in periods shorter than 24 h due to circadian variations of body temperature [16], direct calorimetry is rarely used nowadays. Nonetheless, it can be argued that it is still the gold-standard technique for the assessment of energy expenditure [15].

Indirect calorimetry

Indirect calorimetry estimates heat production from measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) [17]. It is based on the known amounts of heat released per liter of VO_2 and VCO_2 during the combustion of different macronutrients [17]. Importantly, the oxidation of different organic compounds involves different pro- portions of VO_2 and VCO_2, and thus, indirect calorimetry does allow to determine the individual contribution of different macronutrients oxidation to total energy expenditure. Today, two types of indirect calorimeters are widely used: metabolic chambers and metabolic carts [15,18]. Metabolic chambers are airtight rooms, large enough for an individual to live comfortably during periods that usually extend from 12 h to several days. Ambient air is continuously introduced, mixed and with- drawn from the chamber at a constant rate. Gas concentrations of O_2 and CO_2 are determined in the incoming and outgoing air flows after drying it. VO_2 and VCO_2 can be calculated knowing the flow of fresh air and the volume of the chamber [15,18]. The individual's spontaneous physical activity is commonly assessed by motion detectors while in the chamber to determine the different components of energy expenditure. In contrast to metabolic chambers, which are somewhat rare (approximately 30 worldwide [15]) because of their cost and required maintenance, metabolic carts are much more widely used. Metabolic carts are designed to assess respiratory gas exchanges using a ventilated hood or canopy, a facemask or a mouthpiece [18]. Metabolic carts determine VO_2 and VCO_2 capturing expired gases either breath-by-breath or by an open circuit flow (three to five times the volunteer's ventilation) similar to the one used in metabolic chambers [15]. Metabolic carts are easy to use and inexpensive, but limits movement and locomotion, only allowing short-term (up to some hours) assessments. The Deltatrac metabolic cart (DTC; Datex Instrumentarium Corp., Helsinki, Finland), often considered as the gold-standard, is unfortunately no longer manufactured. There are many commercially available metabolic carts on the market [19], although the validity and reliability of some of these instruments are often debatable [19-22].

Doubly labeled water

Ideally, energy expenditure must be calculated from both VO_2 and VCO_2 since the energy equivalent of VO_2 and VCO_2 varies if proteins, carbohydrates or lipids are oxidized.

However, energy expenditure can also be estimated by just VCO_2 with the caveat that speculations have to be made on the source of the macronutrient ratio oxidized [17]. Since the early 1980s, the DLW method has been used to estimate human energy expenditure from VCO_2 [23]. The DLW method relies on the enrichment of the body water with heavy hydrogen (^2H) and heavy oxygen (^{18}O) after drinking an appropriate dose of DLW ($^2H_2{}^{18}O$). After reaching enrichment peaks inversely proportional to total body water, the rate of daily disappearance of both isotopes from the body is determined from collected body fluid samples [23]. VCO_2 is then calculated from the differ-that the respiratory quotient (RQ) is equal to the food quotient, estimated from the diet macronutrient composition. Despite other noncalorimetric methods have been used for assessing VCO_2, such as the labeled bicarbonate [17], the DLW method unequivocally is the reference method for assessing energy expenditure in free living humans [23].

Other methods

Other methods have been used to estimate human energy expenditure, including observed or self- reported physical activity, kinematic recordings (e.g. pedometers, accelerometers) and physiological measurements (e.g. HR, body temperature, galvanic skin response) [14,16]. Despite the rapid growth in commercial activity trackers during the recent years and ongoing efforts for improving energy expenditure estimations [24], the validity of these devices to estimate energy expenditure remains limited [25].

CALCULATION AND INTERPRETATION OF INDIRECT CALORIMETRY

Indirect calorimetry has been used to assess energy expenditure since the time of Lavoisier, but it is in the second half of the 20th century that more precise systems have been developed taking advantage of the tremendously improved sensitivity of flowmeters and gas analyzers [16]. Moreover, indirect calorimetry, ideally in combination with urinary nitrogen, is the only technique that allows precise estimations of the contribution of different energy substrates to energy expenditure. Consequently, indirect calorimetry has become the widely preferred method for assessing human energy expenditure. However, even if indirect calorimetry allows a precise assessment of VO_2 and VCO_2, many sources of error can contaminate and bias the read- outs. A detailed description of how VO_2 and VCO_2 are obtained is beyond the scope of this review and has been recently reviewed [15].

Several equations for assessing energy expenditure from VO_2, VCO_2 and urinary nitrogen were proposed during the 20th century (Table 2). More- over, equations to estimate carbohydrate and fat oxidation have also been derived from the known stoichiometric energy equivalents of O_2 and CO_2 of different macronutrients (Table 2). Since most of urinary nitrogen (>80%) is in the form of urea, the amount of protein oxidation, can be estimated from urinary nitrogen, assuming that 6.25 g of protein are oxidized for every gram of urinary nitrogen.

It should be noted that the stoichiometry of a biomolecule oxidation does not depend on the intermediate metabolic process (e.g. the RQ remains the same if a glucose molecule is completely oxidized within a tissue or if it is converted to lactate in one tissue to be oxidized in another one [26]). Consequently, the equations to estimate energy expenditure

and macronutrient oxidation remain valid regardless of the intermediate metabolic process by which nutrient are oxidized. However, these equations rely on some assumptions and therefore, provide erroneous results when these assumptions are not met. Caution is needed for interpreting these calculations in conditions other than normal physiological circumstances, which are commonly caused by dietary interventions, pathological states and others [16,17].

Macronutrient interconversion

The equations to estimate nutrient oxidation require a more complex interpretation when bio- synthetic process involves biochemical pathways such as lipogenesis or gluconeogenesis [16]. In this case, the result of the calculation does not represent the rate of nutrient oxidation, but the net rate of nutrient utilization regardless of the biochemical pathway [26]. Therefore, whenever lipid synthesis is taking place, the calculated carbohydrate 'oxidation' should be interpreted as the net rate of carbo- hydrate utilization, that is oxidation and conversion to fat. Similarly, when lipogenesis takes place, the fat oxidation equation calculates the net balance between fat oxidation and fat synthesis. In rare cases, calculated fat oxidation may provide negative values when the nonprotein RQ is above 1.0, an indication of net de-novo lipogenesis (i.e. the rate of lipogenesis exceeds the rate of fat oxidation). Conversely, when gluconeogenesis from amino acids takes place (lactate and pyruvate conversion to glucose does not affect any of the calculated substrate oxidation), the calculated value for carbohydrate oxidation reflect the net rate of carbohydrate disappearance (i.e. oxidation – synthesis). In this circum- stance, the rate of fat oxidation rate will be slightly underestimated by approximately 10% of the rate of glucose synthesis [26]. Protein oxidation rate will similarly be affected, since urinary nitrogen will be the consequence of not only protein oxidation, but also alanine deamination. Importantly, although de-novo lipogenesis does not affect the calculation of total energy expenditure, it is slightly affected when gluconeogenesis takes place.

Generation of intermediate metabolites

An important assumption of the macronutrient oxidation equations is that there is no accumulation or excretion of any intermediate metabolite, and there- fore, oxidation leads only to the production of end products such as CO_2, water and urinary nitrogen [26]. Therefore, whenever changes occur in the body pool or the excretion rate of intermediate metabolites, the interpretation of indirect calorimetry should be made with caution [17]. The CO_2 body pool is physiologically well maintained but can be impacted soon after intense exercise, during hyper or hypoventilation or as a consequence of a shift in acid–base balance [16,26]. Under these circumstances, indirect calorimetry calculations are likely invalid and misleading, and should be discussed accordingly. In case of a decreased body urea pool, protein oxidation will be proportionally overestimated [16]. Similarly, erroneous results are generated in the presence of metabolic processes that produce significant amounts of nitrogenous end products other than urea, such as uric acid (RQ = 0.707) or ammonia (RQ = 0.950) [17].

Another cause of erroneous estimations can be the accumulation of intermediate metabolites such as lactate or ketone bodies [17,27]. Corrections can be made in the nutrient oxidation

equations to account for changes in circulating, urine and breath levels of intermediate metabolites [17,27]. However, it should be noted that even if it can be considered in the calculation, a change in lactate or ketone bodies concentration will be coupled with an increase pro- duction of hydrogen ions, which is likely to produce CO_2 retention.

Alcohol intake

The nutrient oxidation equations assume that the oxidation mixture is composed of carbohydrates, fat and proteins. However, if alcohol is ingested, it will be preferentially oxidized since it cannot be stored within the body. Since alcohol is rapidly oxidized, alcohol intake provides a good estimation of alcohol oxidation and can be used to correct the calculation of the other nutrient oxidation rates [17].

Type of macronutrient ingested

One should realize that the equations to calculate macronutrient oxidation rates were built assuming a single representative value for the energy equivalents of O_2 and CO_2. However, the real energy equivalents of O_2 or CO_2 depend on the type of biomolecules being oxidized, so the composition of uncommon nutrient intake does introduce minor errors in the estimation of energy expenditure. For instance, while the RQ for fat oxidation is normally considered at 0.71, the oxidation of medium chain triglycerides provides an RQ of 0.74 [17]. Similarly, the oxygen consumed per gram of nutrient can be underestimated depending on the dietary source of protein and carbohydrates. For instance, zein protein oxidation consume 9% more oxygen than the one considered by the standard values, while sucrose or lactose oxidation underestimate the carbohydrate oxidation up to 6% [16].

Oxygen consumption estimation from carbon dioxide production

As mentioned above, the food quotient is commonly used for estimating RQ when energy expenditure is calculated only from VCO_2 such as with the DLW method. It should be noted however, that the food quotient is equal to RQ only under conditions of energy and macronutrient balance [17,28▪,29▪]. Therefore, corrections are needed for estimating VO_2 from VCO_2 measurements when the individual is in positive (the RQ will be higher than the food quotient) or negative (the RQ will be lower than the food quotient) energy balance [17,28▪,29▪].

CONCLUSION

The assessment of energy expenditure and macro- nutrient oxidation is of great relevance in the obesity research field. Indirect calorimetry, the reference method, enables the calculations of energy expenditure and macronutrient oxidation in confined conditions, while the DLW is the preferred method to assess energy expenditure in free living conditions. Both methods imply simple calculations using VO_2 and/or VCO_2. However, these calculations can provide erroneous results and/or require more complex interpretation when several physiological processes, often elicited by dietary interventions, take place.

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28. Hall KD, Guo J, Speakman JR. Do low-carbohydrate diets increase energy & expenditure? Int J Obes (Lond) 2019; 43:2350–2354. [PubMed: 31548574] ▪In this commentary, Hall et al. reexamined previous data in regard to the effect of low-carbohydrate diets on energy expenditure. They illustrate that failing to capture the real respiratory quotient might change the overall conclusion of a study using doubly labeled water to assess energy expenditure.

29. Hall KD, Guo J, Chen KY, et al. Methodologic considerations for measuring energy expenditure differences between diets varying in carbohydrate using the doubly labeled water method. Am J Clin Nutr 2019; 109:1328–1334. [PubMed: 31028699] ▪The study analyzed changes in energy expenditure in response to a ketogenic diet. Although no effect was detected by indirect calorimetry, the doubly labeled water method showed a marked increase in energy expenditure, which was attenuated when it was corrected for the diet induced respiratory quotient. This constitutes a good example of the need of conducting proper corrections when the basic assumptions of the methods for assessing energy expenditure are not met.

KEY POINTS

- Indirect calorimetry, either using a metabolic chamber or a metabolic cart, is the preferred method to assess human energy expenditure and is the only method enabling the assessment of macronutrient oxidation.
- Unlike indirect calorimetry, the doubly labeled water method allows an accurate calculation of human energy expenditure under free living conditions.
- Indirect calorimetry and the doubly labeled water method imply simple calculations using oxygen consumption and/or carbon dioxide production. However, these calculations can provide erroneous results and therefore require corrections or more complex interpretation in presence of unusual biochemical pathways. This is elicited during prolonged fasting or overfeeding as well as in response to extreme dietary composition.
- Dietary interventions and nutritional status can affect the calculations of energy expenditure and macronutrient oxidation when eliciting processes such as gluconeogenesis, lipogenesis, ketogenesis, alcohol oxidation, under and overfeeding.

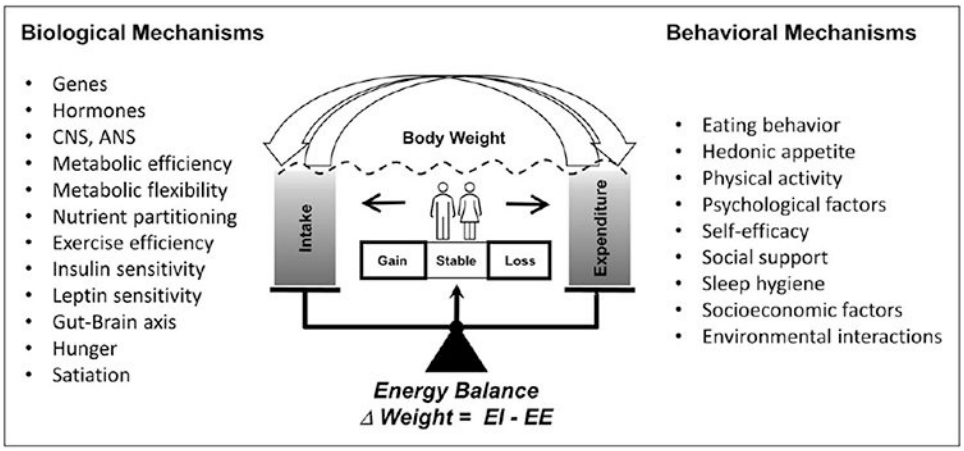

FIGURE 1.

Determinants of human body weight regulation. Despite a strong homeostatic regulation of energy balance, biological and behavioral factors can perturb its regulation. Therefore, the variations on body weight are explained by complex interactions between the individual's genetic background, environmental, behavioral and socioeconomic factors.

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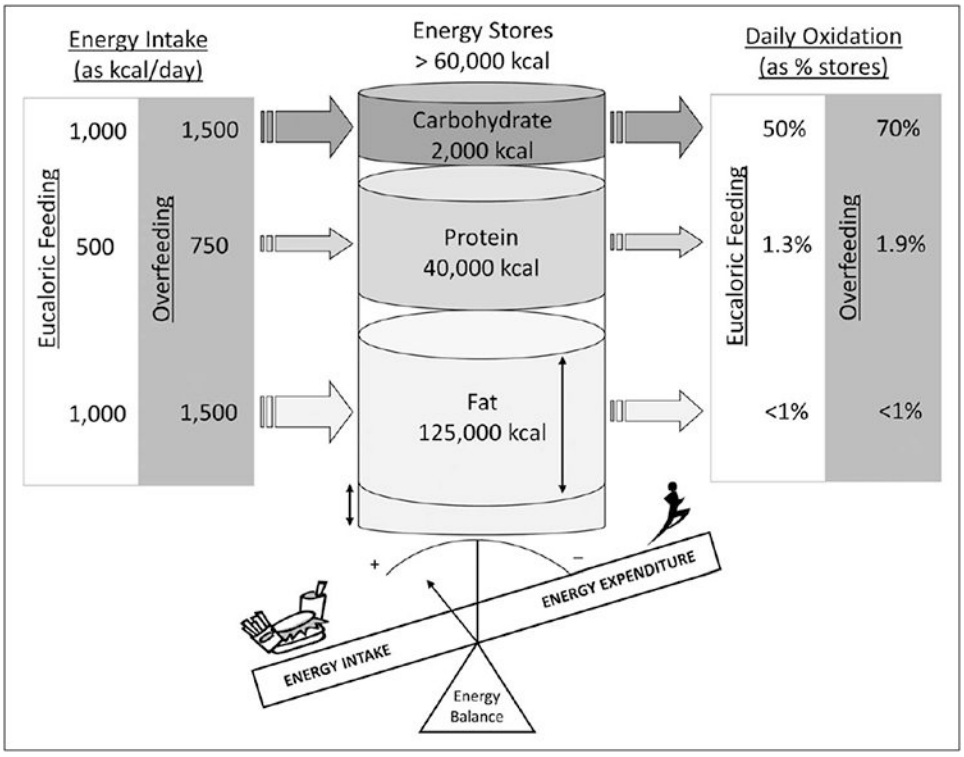

FIGURE 2.

Energy balance. In humans, energy balance depends upon the separate maintenance of macronutrient balance. The daily turnover of carbohydrates is around 50% of the body reserves in energy balance conditions and can be increased up to 100% under overfeeding circumstances. Daily protein turnover typically represents a bit more than 1% of the body reserves and is directly determined by protein ingestion resulting in a robust maintenance of body protein stores. Daily fat turnover represents less than 1% of the fat body reserves. Importantly, while changes in carbohydrate and protein intakes are rapidly mirrored by proportional changes in their oxidation, changes in fat intake are not rapidly compensated by changes in fat oxidation. Therefore, both carbohydrate and protein balances are well regulated and do not impact much the overall energy balance. In contrast, fat balance is the main determinant of energy balance in humans. Adapted from [13].

Table 1.

Comparison of methods to assess human energy expenditure

Method	Duration of use	Accuracy	Cost	Advantages	Limitations
Direct calorimetry	One to several days	High except for thermal inbalance conditions	High (set up and maintenance)	Direct measure of heat production, complete control of environmental factors	Technically demanding, unable to detect acute changes, restricted to confined space
Indirect calorimetry, metabolic chamber	Hours to several days	High	High (set up and maintenance)	Real-time minute-by-minute data, allow measurement of components of energy expenditure and macronutrient utilization	Technically demanding, restricted to confined space
Indirect calorimetry, metabolic cart	Hours	High for RMR, moderate for other components of 24 h EE	Moderate (set up and maintenance)	Quick response time, easy to operate, feasible in clinical setting, allow measurement of macronutrient utilization	Restricted mobility
DLW	4-21 days	Pretty high	High (isotope cost and analysis)	Gold standard in free-living conditions, applicable to wide range of protocols	No time-course data, unable to differentiate components of EE unless combined with chamber
Physical activity log	Flexible	Low	Low	Easy to administer	Participant burden may compromise data quality and some physical activities (e.g. cycling) are difficult to detect
Kinematic measurements	Flexible	Low	Low	Easy to administer, objective and unbiased	Pedometers provide no data on patterns and intensity of physical activity
HR monitoring	Flexible	Low	Low	Easy to administer, objective and unbiased	Requires individualized calibration, significant loss of data points
Ventilation monitoring	Hours	Low	Low	Easy to administer, objective and unbiased	Low applicability in free-living conditions

DLW, doubly labeled water; EE, energy expenditure; HR, heart rate. Adapted from [14].

Table 2.

Commonly used equations for estimating energy expenditure, carbohydrates oxidation and fat oxidation

Author	Equation
Energy expenditure	
Weir	EE = 3.941_x VO_2+1.106_x VCO_2 −_2.17 x N
Consolazio	EE = 3.78 x VO_2 + 1.16 x VCO_2 − 2.98 x N
Brouwer	EE = 3.866 x VO_2 + 1.20 x VCO_2 − 1.43 x N
Jequier	EE = [4.686 + 1.096_(NPRQ x 0.707)] x $NPVO_2$ + 4.60 x PVO_2
Ferrannini	EE = 3.91 x VO_2 + 1.10 VCO_2 − 3.34 x N
Carbohydrates oxidation	
Jequier	CHOox = 4.113 x VCO_2 − 2.907 x VO_2 − 0.375 x PROox
Frayn	CHOox = 4.55 x VCO_2 − 3.21 x VO_2 − 2.87 x N
Fat oxidation	
Jequier	FATox = 1.689 x VO_2 − 1.689 x VCO_2 − 0.324 x PROox
Frayn	FATox = 1.67 x VO_2 − 1.67 x VCO_2 − 1.92 x N

CHOox, carbohydrates oxidation (g/min); EE, energy expenditure (kcal/min); FATox, fat oxidation (g/min); N, urinary nitrogen (g/min); NPRQ, nonprotein respiratory quotient; NPVO2, nonprotein oxygen consumption (l/min); PROox, protein oxidation (g/min); PVO2, protein oxygen consumption (l/min); VCO2, carbon dioxide production (l/min); VO2, oxygen consumption (l/min).