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PII: S0261-5614(20)30616-6

DOI: https://doi.org/10.1016/j.clnu.2020.11.012

Reference: YCLNU 4567

To appear in: *Clinical Nutrition*

Received Date: 10 July 2020

Revised Date: 18 October 2020

Accepted Date: 10 November 2020

Please cite this article as: Bendavid I, Lobo DN, Barazzoni R, Cederholm T, Coëffier M, Schueren Mdvd, Fontaine E, Hiesmayr M, Laviano A, Pichard C, Singer P, The centenary of the Harris-Benedict equation: How to assess energy requirements best? Recommendations from the ESPEN Expert Group, *Clinical Nutrition*, https://doi.org/10.1016/j.clnu.2020.11.012.

The centenary of the Harris-Benedict equation: How to assess energy requirements best? Recommendations from the ESPEN Expert Group

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Word count (excluding title page, abstract, references, figure legends, tables and acknowledgements): 5613

No. of Figures: 3, No. of Tables: 5

List of abbreviations

ADP – adenosine diphosphate

ATP – adenosine triphosphate

BIA – bioelectrical impedance analysis

BMI – body mass index

CT – computed tomography

DXA – dual-energy X-ray absorptiometry

ESPEN – European Society for Clinical Nutrition and Metabolism

FAD – flavin adenine dinucleotide

FFM – fat free mass

GLIM – Global Consensus for Diagnosing Malnutrition

ICU – intensive care unit

NAD – nicotinamide adenine dinucleotide

REE – resting energy expenditure

RQ – respiratory quotient

WHO – World Health Organization

Abstract

Background and aims: The year 2019 marked the centenary for the publication of the Harris and Benedict equations for estimation of energy expenditure. In October 2019 a Scientific Symposium was organized by the European Society for Clinical Nutrition and Metabolism (ESPEN) in Vienna, Austria, to celebrate this historical landmark, looking at what is currently known about the estimation and measurement of energy expenditure.

Methods: Current evidence was discussed during the symposium, including the scientific basis and clinical knowledge, and is summarized here to assist with the estimation and measurement of energy requirements that later translate into energy prescription.

Results: In most clinical settings, the majority of predictive equations have low to moderate performance, with the best generally reaching an accuracy of no more than 70%, and often lead to large errors in estimating the true needs of patients. Generally speaking, the addition of body composition measurements did not add to the accuracy of predictive equations. Indirect calorimetry is the most reliable method to measure energy expenditure and guide energy prescription, but carries inherent limitations, greatly restricting its use in real life clinical practice.

Conclusions: While the limitations of predictive equations are clear, their use is still the mainstay in clinical practice. It is imperative to recognize specific patient populations for whom a specific equation should be preferred. When available, the use of indirect calorimetry is advised in a variety of clinical settings, aiming to avoid under- as well as overfeeding.

Keywords: energy expenditure; predictive equations; indirect calorimetry; energy requirements; nutritional prescriptions

1. Introduction

J. Arthur Harris and Francis G. Benedict published their landmark study, entitled “A Biometric Study of Basal Metabolism in Man” in 1919 [1] and a shorter paper the previous year [2]. These were based on data gathered using “an apparatus for studying the respiratory exchange”, published a decade earlier (**Figures 1 and 2**) [3]. Data have been accumulating since, showing a good relationship between energy expenditure measured by indirect calorimetry and predicted energy expenditure using the Harris-Benedict equations in non-obese normal volunteers and even more so in subjects with obesity.

The European Society for Clinical Nutrition and Metabolism (ESPEN) organized a Scientific Symposium celebrating the centenary of the Harris-Benedict equations and an expert group met in Vienna, Austria on October 27 and 28, 2019. The group examined the development of predictive equations for the measurement of resting energy expenditure and the use of indirect calorimetry. It critically examined the clinical parameters influencing energy expenditure and the relevance and utility of using measured and predicted energy expenditure to direct nutritional therapy in adult patients of different ages, in different settings, and going through various disease processes. This position paper is based on presentations and discussions at the Vienna Symposium, along with a subsequent update of the literature.

2. Historical landmarks

Historical landmarks surrounding the science of measuring energy expenditure are summarized in **Table 1** [1-10].

3. Energy balance

Energy balance is the difference between intake and expenditure. About two thirds of energy expenditure is resting energy expenditure, which accounts for vital functions at rest. About 20-30% is activity-related, more in young active patients and less in older and more sedentary adults, while 5-10% is used for thermogenesis. Indirect calorimetry measures oxygen consumption and carbon dioxide production to calculate energy expenditure. Energy expenditure includes thermogenesis, which corresponds with the energy dissipated by metabolic processing of substrates (protein, carbohydrates, fat) and diet-induced thermogenesis (food, drinks). The type and rate of substrate utilization are reflected by the respiratory quotient (RQ), calculated by the division of carbon dioxide production by oxygen consumption (VCO_2/VO_2). This is different for each substrate: 1 for carbohydrate, 0.8 for protein, 0.7 for fat and approximately 0.85 for a combined diet. Optimally, indirect calorimetry should be used to provide measurements instead of predictive equations, making for a more exact energy balance. However, survey showed that as indirect calorimetry was not available to 80% of nutrition staff members, only estimated values were used [11].

4. The accuracy of predictive equations according to weight

Predictive equations for resting energy expenditure are based on anthropometrics (weight, height, BMI or fat free mass), age, sex, disease-related conditions or combinations of these factors [1, 2, 12-15]. Estimations are generally considered accurate if they fall within an error range of 10% when compared with indirect calorimetry. Age affects prediction errors significantly, and the same holds true for extremes of weight or extreme disease states (tetraplegia, high fever, etc.). Ethnicity may also affect the accuracy of predictive equations, as demonstrated in a recent study among Chilean non-whites, in whom predictive equations generally performed poorly [16]. Looking at the predictive equations available currently, some take into account only anthropometric factors (sex, age, weight, height) [1, 2, 13, 15], while others require body composition assessment (FFM and/or fat mass) [14, 17-21]. Several equations use different adjustment factors according to age (e.g. Henry equation [12]) or BMI (e.g. Müller equation [14]). To evaluate the accuracy of predictive equations, measured resting energy expenditure (by indirect calorimetry) has been compared with predicted resting energy expenditure in health and in different clinical conditions. The Harris-Benedict equations perform reasonably well in those with obesity, being accurate in 68.5% of patients with a BMI between 25 and 40 kg/m^2 and 62.4% of patients with a BMI above 40 kg/m^2 [22]. Surprisingly, the Bernstein equation [17], originally devised for patients with obesity, actually had the worst predictive abilities, with only 23% accurate predictions [22]. In a recent study, 33% of all predictions were inaccurate, with the best reaching only 60% accuracy across weight groups [22]. Other studies have reported similar results [23, 24].

Eighteen different equations were compared with indirect calorimetry in ventilated patients, and the mean error was 233-426 kcal/day [25]. Even the better functioning equations were accurate in only half of the patients, with both over- and underestimations. In this study, the World Health Organization (WHO) equations [15] performed best among the lean (BMI <18.5 kg/m^2), while in patients with obesity (BMI >30 kg/m^2) the Harris-Benedict equations were the most accurate. Kruzienga *et al*. [26] found similar results in hospitalized patients, and advised that the WHO equations [15] should be used for those with a BMI <30 kg/m^2 and the Harris-Benedict equations for those with BMI >30 kg/m^2. However, these findings and recommendations are not unanimous. For example, Weijs [24] found the Mifflin equation [13] to be the most accurate among obese US adults, and no single equation was accurate among Dutch adults who with overweight or obesity, leading him to recommend the WHO equations [15] for overweight adults and the Lazzer equations [19, 21] for patients with obesity.

In healthy, normal-weight adults, the Harris-Benedict equations [1, 2] appear to be among the best equations to predict resting energy expenditure [22]. However, the accuracy of the Harris-Benedict equations is reduced in older people [27] or in patients with low [22, 26] or high BMI [22, 24]. Interestingly, in patients with obesity resting energy expenditure is decreased after major weight loss induced by bariatric surgery [28]. While energy expenditure remains proportional to body weight, estimation equations become less accurate (around 60% at best) in patients with obesity [29]. In this context, some equations [1, 2, 14, 30] exhibit a marked reduction in their accuracy to predict resting energy expenditure while others are more accurate [13, 19, 21, 29]. However, at least 50% of patients have an inaccurate prediction of resting energy expenditure irrespective of the equation used. As already mentioned, a low body weight is also associated with inaccuracy of the Harris-Benedict equations [26]. In severely malnourished patients with anorexia nervosa, the most accurate prediction is around 45% [22], showing that predictive equations are not appropriate for the prediction of resting energy expenditure at extremes of BMI at the individual level. Moreover, acute and chronic diseases also affect energy needs and an activity factor has bee suggested. It was estimated at 1.5 for healthy subjects, 1.3 in acute and chronic illness and 1.1 in critical illness, but as these numbers are hypothesized rather than proven [31], their use cannot yet be generally recommended. However, the clinician may assume that total energy expenditure is reduced or normal in the various chronic illnesses, and is not elevated during illness. Nevertheless there are wide variations. In adult patients with head and neck cancer, Souza et al. [20] also showed that the Harris-Benedict equations exhibited a wide range of limits of agreement and thus proposed a new equation. In patients with lung, rectal, colon or pancreatic cancer, all tested predicted equations (including Souza-Singer equation [20]) show insufficient accuracy even if body composition factors were included [32]. Underestimation is all too common (15-20%) in patients with cancer [32] and predictive equations needs careful interpretation to avoid under- or overestimation of energy requirements.

Hence, a tendency to prescribe fewer calories than required is noted in patients with obesity when using equations. The Harris-Benedict equations are [1, 2] still among the better equations for estimation of energy expenditure in healthy subjects, although its accuracy decreases in those with obesity or underweight, the acutely or chronically ill and the elderly (**Figure 3**) [22, 24, 26, 32-39]. Other equations may perform slightly better in specific populations [13, 15, 19, 21], but resting energy expenditure cannot be predicted accurately for each individual, and indirect calorimetry is recommended to evaluate energy requirements.

5. Energy expenditure measured by oxygen utilization

Energy is derived from hydrogen by metabolic processes that require oxygen. In a complex process, the protons that shuttle due to a gradient are the motor for adenosine triphosphate (ATP) generation from substrates. The transmembrane movement of protons back into mitochondria through the ATP-synthase then drives the production of ATP from adenosine diphosphate (ADP) [40].

Direct calorimetry measures heat released from metabolic reactions, while indirect calorimetry measures utilization of oxygen and elimination of carbon dioxide. Fat yields more calories per gram utilized, resulting in a lower RQ. The likely cause is that glucose metabolism heavily relies on nicotinamide adenine dinucleotide (NAD), while metabolism of fat uses relatively more flavin adenine dinucleotide (FAD). It is worth noting that in terms of ATP production via oxygenation, glucose is the most efficient, yielding 120 kcal per liter of oxygen, compared with 100 kcal from fat. Energy metabolism consists of three steps: (1) the release of hydrogen from water and nutrients, (2) production of a proton gradient during cell respiration, and (3) production of ATP by consumption of this proton gradient. In practice what is actually measured is the amount of oxygen consumed for energy production. Measuring the amount of ATP produced is not yet possible.

Organs utilize energy at different rates. Relative to their mass, the heart and the kidneys have the highest energy consumption, with the brain and liver following suit. Muscle, fat and bone lag behind. Resting energy expenditure is closely correlated with fat free mass (FFM). However, as the size of the body increases, the viscera contribute relatively less to the resting energy expenditure while the contribution of the muscle and fat grows. Age influences the relative contributions of the different organs as well. Although measuring FFM in critically ill patients to define the required amount of nutrients makes sense, very little evidence actually exists to support this approach, and FFM is mainly used to prescribe substrates in overweight and subjects with obesity.

6. Body composition and predictive equations

The human body may be divided into three compartments – FFM, fat and bone. FFM and bone are responsible for an energy expenditure of approximately 14.5 kcal/kg/day, while fat only requires about 4.5 kcal/kg/day [41].FFM is a heterogeneous compartment in terms of energy expenditure. Some components have higher metabolic rate than others. Gallagher *et al*. [41] report that muscles are responsible for about 22.5% of resting energy expenditure while muscles represent 50.4% of FFM. In contrast, heart, kidneys, liver and brain are together responsible for 58% of resting energy expenditure whereas these organs only represent 6.9% of FFM. During weight changes, the components of FFM, i.e. different organs, are not similarly affected and their energy demands are altered in different ways. For instance, in older people, muscle mass is reduced compared with young people while non-muscular FFM is not altered. Similarly, in patients with cancer, muscle mass decreases but tumor cells or metastases can increase REE of non-muscular fat-free mass. A few predictive equations such as the Bernstein [17], Müller [14], Huang [18], Lazzer [19, 21] and Owen [42, 43] equations incorporate FFM. It should, however, be interesting to investigate further whether new body composition-based equations, considering not only FFM but muscle mass and non-muscular FFM, are more robust in predicting resting energy expenditure. The available methods to assess body composition are described in **Table 2**.

The more readily available methods are discussed in detail, including their applicability in specific patient populations.

Dual-energy X-ray absorptiometry (DXA) measures three compartments: fat mass, lean mass and bone mass. It is a fast and noninvasive method that exposes the patient to acceptable radiation doses (2-5 µSv). It also allows the measurements of segmental body composition, such as visceral fat mass and appendicular skeletal muscle mass. There is variability between different devices and manufacturers [44, 45], and hydration status influences results as well [46].

Bioelectrical impedance analysis (BIA) uses hand to foot surface electrodes, with several methods available of either single or multiple frequencies. It is also fast and noninvasive and provides raw electrical data- reactance, resistance and impedance. In fact, BIA only determines fluid related compartments, i.e. FFM, and this compartment may be further divided into body cell mass and extracellular mass. Fat is obtained by subtraction of FFM from body weight. Contrary to common belief, BIA does not directly measure fat mass. Several BIA equations are available. However, fluid status can have major effects on BIA readings [47], and the same is true for patient position [48]. Aside from phase angle measurements, it is probably inadequate for use in critically ill patients [49, 50].

Looking at the performance of DXA and BIA [51], DXA identifies higher fat mass than BIA. When both methods were compared according to BMI [52], larger variations were apparent at both extremes of BMI. As a result, it is not safe to clinically compare data from DXA and BIA, irrespective of which BIA equation is used. An analysis of the performance of the different equations to calculate FFM from BIA [53] suggests Sun's equation [54] is the most appropriate for studies at the population level. In 2018, Tewari *et al*. [55] published a comparison of three methods for assessment of body composition, DXA, BIA and computed tomography (CT). Results were widely distributed, suggesting that variation between methods is high.

Differences between DXA and BIA, manufacturers and devices must be taken into account and results should be interpreted accordingly. The approach should probably be longitudinal, as results might be confounded by factors such as hydration status.

The addition of FFM to weight-based equations did not provide further advantage in overweight subjects, even when different methods for FFM measurements were used. This lack of added benefit was apparent in subjects with obesity [24] as well as those who were underweight (BMI <16 kg/m^2) [22]. When patients with cancer were examined, equations using FFM were not among the better performing; a new equation, developed by Souza-Singer *et al*. [20], was intended specifically for this population, but remains to be validated. As mentioned previously, weight-based predictive equations for resting energy expenditure show a decrease of accuracy during weight changes (underweight or overweight), with aging or during acute or chronic diseases. It is well established that body compartments differently affect resting energy expenditure. Indeed, FFM is the major determinant of resting energy expenditure while fat mass influences resting energy expenditure only slightly. There is a close correlation between FFM and resting energy expenditure. CT is an interesting method to evaluate or diagnose reduced muscle mass but it is not appropriate to predict resting energy expenditure. Bernstein *et al*. [17] used total body potassium technique, while Müller *et al*. [14], Lazzer *et al*. [19, 21] and Huang *et al*. [18] used BIA. Mifflin *et al*. [13] used skinfold thickness and circumference approach and Owen *et al*. [42, 43] used hydrostatic weighing. Interestingly, some studies compared the accuracy of weight-based equations to body composition-based equations [22-24, 32]. In patients who are overweight and those with obesity, Weijs [24] reported that in the Dutch cohort (n=208) with body composition data, all tested body composition-based equations showed a decrease in accuracy of prediction when compared with weight-based equations, except for Bernstein equations [17]. In a large cohort of patients with grade I and II obesity (n=1735), the accuracy of prediction was not improved by body composition parameters, irrespective of the technique used to measure body composition (BIA or DXA), except for Müller equation [56]. Marra *et al*. [23] observed similar results. Concerning patients who are underweight, body composition-based equations did not exhibit better results than weight-based equations [22]. Similarly, in cancer patients, no improvement in prediction of resting energy expenditure was observed with body composition-based equations [32]. All these data suggest that body composition-based equations do not improve prediction of resting energy expenditure whatever the clinical conditions (overweight, underweight, chronic diseases).

The ESPEN consensus statement from 2015 [57] identified three factors as having strongest agreement as related to malnutrition: weight loss, reduced BMI and reduced lean body mass. Most societies encourage using lean or FFM as a crucial phenotypic criterion for malnutrition. The Global Consensus for Diagnosing Malnutrition (GLIM) consortium [58, 59]. is an initiative to provide a consensus on the diagnosis and grading of malnutrition, and one of its goals is clinical guidance for severity grading on low muscle mass. Malnutrition may be graded according to severity as moderate/stage 1 and severe/stage 2 [58, 59]. FFM serves as an important criterion for this grading system, as low muscle mass is one of the three phenotypic criteria, alongside weight loss and low BMI. These are complemented by two etiological criteria: reduced food intake/assimilation and the presence of inflammation. FFM may be assessed by various methods. DXA and BIA as well as calf circumference have been incorporated into the severity assessment criteria, and the future may see the addition of others, such as ultrasound [60], CT at the L3 vertebral level [61] and the D_3 creatine dilution test [62].

7. Predictive equations and indirect calorimetry in critical illness

When compared with measurements, there is a large variation in the accuracy of the Harris-Benedict equations [1, 2], in relation to numerous variables, both inherent and acquired – genetics, muscle mass, hormones, medications, physical activity, dietary intake, etc. [63]. Even a century ago, Harris and Benedict [1, 2] considered regression equations as having limited trustworthiness due to their high variation, and so regression equations should not be used to predict individual resting energy expenditure [2, 64]. Predictive equations may offer merely the illusion of accuracy and precision, and so indirect calorimetry should be used to measure resting energy expenditure whenever possible instead. Commonly used equations such as the Mifflin [13], Ireton-Jones [65] or Faisy-Fagon [66] equations, to name but a few, are not very accurate and one may also discover high variation between methods. It should be emphasized that an equation devised at a certain center may perform poorly elsewhere. Put together, even the best performing predictive equations reach an accuracy of only 50-70%. Using mean values may lead to very high rates of inaccuracy, with most patients receiving either hyper- or hypocaloric nutrition [36], without one universally applicable prescription. Even weight in itself carries many inherent problems in the ICU, including methods for its measurement/estimation or changes in fluid balance. Estimating energy expenditure at the extremes of weight is even less accurate. Different illnesses and disease states make quantification yet harder. Sepsis has varying effects on energy expenditure according to its phase, type and severity.

Oxygen consumption (VO_2) obtained from a pulmonary artery catheter, using a multiplier of 7, may estimate energy expenditure well. Carbon dioxide production (VCO_2), easily obtained from the ventilator and using a multiplier of 8.2, is more readily available compared to VO_2 [67], although it is definitely not optimal [68, 69]. Weir's equation [70] for energy expenditure, originally described in 1949, is

$$\text{Energy expenditure (kcal/day)} = [(VO_2 \times 3.941) + (VCO_2 \times 1.11) - (\text{urinary } N_2 \times 2.17)]$$

As the effect of protein metabolism, i.e. nitrogen, on this equation is very small, it is largely disregarded. This means using an indirect calorimeter, VO_2 and VCO_2 obtained from a ventilator in mechanically ventilated patients or using a canopy in spontaneously breathing subjects may be measured, and the almost exact energy expenditure (disregarding protein metabolism) can be calculated. As VO_2 has a multiplier of 3.94 and VCO_2 has a multiplier of 1.11, errors in VO_2 readings have four times more impact on the result compared with VCO_2. If energy expenditure is calculated using either VO_2 or VCO_2 alone, a stable and known RQ is required.

There are many conditions that may limit or prohibit the use of indirect calorimetry. Still, considering the negative impact of an accumulating energetic deficit [71], the accuracy of indirect calorimetry outweighs these disadvantages [72]. Practitioners need to become accustomed to this technology including the proper way to use it and how to cope with its limitations [73]. Different indirect calorimetry instruments come with their particular methods and pitfalls. Lastly, one must not forget the variation in protein as well as caloric needs across disease states. The benefits and limitations of indirect calorimetry and predictive equations are summarized in **Table 3**.

8. Obesity

Resting energy expenditure increases with body weight, but activity energy expenditure does to a much lesser extent [74]. Evidence points towards higher activity energy expenditure in people with obesity for the same level of exercise, but this is offset by generally lower levels of activity [75]. When diet-induced thermogenesis was measured [76], the difference between subjects with and without obesity was negligible – only 4 kcal/day! As a result, we must be careful if crudely estimating it as 10% of total energy expenditure.

Therefore, in patients with obesity: (1) basal/resting energy expenditure increases, (2) diet-induced thermogenesis decreases relatively, and (3) activity energy expenditure increases for the same exercise but decreases due to lower activity levels. Evaluation of total energy expenditure in the patient with obesity should take the level activity into consideration.

9. The elderly

In the elderly, activity energy expenditure is lower. Relative to body weight, resting energy expenditure is slightly elevated in lean subjects (BMI <21 kg/m^2) [77], most likely due to reduced fat and muscle tissue and the relative contribution of organs with a high metabolic rate. Compared with indirect calorimetry, the Harris-Benedict equations performed well in elderly patients, and when measuring FFM, the Mifflin-St. Jeor equation [13] was even more accurate [77].Current ESPEN guidelines for nutritional support in the elderly [78] advocate: (1) Routine screening by systematic assessment, (2) provision of calories – 30 kcal/kg/day and protein – 1 g/kg/day, (3) targeting malnourished patients with specific calorie and protein goals, (4) specific recommendations for specific diseases, and (5) hydration – drinking 1.6 L/day for women, 2 L/day for men.

In elderly patients hospitalized for various reasons, providing energy, protein and vitamin supplementation resulted in halving 3-month mortality rates [79]. In the EFFORT trial [80, 81], individualized nutritional support to 2,088 medical inpatients reduced mortality rates as well as the need for readmissions and improved functional capabilities. A key element to this success was the evaluation of energy requirements using the Harris-Benedict equations or indirect calorimetry.

Multiple factors may interact to produce a catabolic response, in turn translating into poorer outcomes. These include disease-related malnutrition, with or without inflammation; frailty/gerasthenia; osteoporosis; and sarcopenia. Over 50% of older hospitalized patients display 2 or 3 of these syndromes concomitantly. Malnutrition may be related to an illness but may also present independently. It is postulated that the negative effects of disease with inflammatory components are greater than those of non-inflammatory nature (**Table 4**). It is of importance to recognize diseases with or without inflammation since this may affect REE.

10. The surgical patient

Sir David Cuthbertson was the first to demonstrate in trauma patients that the direct injury to the tissue was not in itself the main cause for nitrogen loss [82, 83]. Nitrogen loss in urine peaked during days 3-8 following injury, the main source for which was breakdown of skeletal muscle.

The response to surgical stress was described in ebb and flow stages. During the ebb stage, lasting minutes to hours, the metabolic rate goes down, with reciprocating decreases in oxygen consumption and temperature. The flow phase begins later and lasts days to weeks, characterized by elevations in the metabolic rate and protein catabolism as well as a tendency for water and sodium retention. These are followed by a convalescence phase which is anabolic in nature, during which the patient usually excretes excess water and sodium [84].

During the acute phase weight generally increases owing to fluid retention, goes down during the post-acute phase and again up during the anabolic convalescence phase due to increase in FFM. The need for nutritional therapy increases with duration of acute illness and if not systematically provided life-threatening severe malnutrition will develop. As some patients undergoing major abdominal surgery are unable to maintain sufficient food and water intake, and as they have increased rates of vomiting, they are particularly prone to the development of nutritional deficiencies [85]. While providing nutrition, care must be taken to prevent the refeeding syndrome that may send the patient into a state of multiple organ dysfunction, harming the heart, brain and liver and exerting many other deleterious effects [86].

In order to improve the applicability of predictive equations during these changes, factors often referred to as "stress factors" have been applied. An example is the Schofield adaptation of the Harris-Benedict equations: +10% for each 1°C elevation of temperature, +10% for diet-induced thermogenesis and +10 to 50% for stress. A different approach was to adapt for levels of activity, between -10% for a mechanically ventilated patient up to +40% for patients up around the ward [87]. However, all of these numbers are purely speculative with practically no proof for their utility. Not only severity and stage of illness but also medical treatment carries an effect on energy requirements [88, 89]. There is, therefore, a role for indirect calorimetry in selected patients. It seems very few patients require more than 2,000 kcal/day, above which the danger of overfeeding becomes serious.

In the absence of available indirect calorimetry, the Ireton-Jones [45] or the Penn-state [90] equations are generally preferred in surgical or trauma patients, but estimates of 25-30 kcal/kg/day may be used to begin with and then changes according to nutritional parameters. A recent study found that the resting energy expenditure did not vary greatly in the first few days following major abdominal surgery [91]. Only a third of the patients had a greater than 10% elevation in their REE, and as it seems energy requirements generally do not go up during the first few days after surgery, nutrition should be prescribed accordingly. When prescribing nutrition for the surgical patient, one must keep in mind there is currently no high-quality published evidence that measurement of energy requirements to inform nutritional therapy in surgical patients impacts on outcome.

11. Cancer

In most countries, cancer rates are rising as life-span increases [92]. It has been shown that cancer exerts extensive metabolic effects [93], with the pooled effect of body mass loss and reduced survival in those patients [94]. Cancer cells influence different host tissues and organs, making it a systemic disease. Tumor stage and inflammation are key drivers of hypermetabolism. In patients with advanced cancer, those who lost more than 5% body weight had significantly lower survival rates [95-98]. Patients with cancer cachexia receiving nutritional interventions had better prognosis when compared with controls [99], and patients with cancer adhering to the nutrition and physical activity endorsed by the American Cancer Society had better survival when compared with those who did not [100]. ESPEN has published guidelines for nutritional therapy in this patient population, including delivery of energy 25-30 kcal/kg/day and protein 1-1.5 g/day. However, any guideline may not capture the short- and long-term fluctuations of energy expenditure and may lead to suboptimal support. A key driver of malnutrition is the hypermetabolic state of these patients, which is related to poorer outcomes and reduced response to therapy [101]. Large variability exists in this aspect, and assessment of energy expenditure is difficult. Muscle mass is a key factor, both in quantity (mass) and quality (fatty infiltration or myosteatosis), making the effect on total energy expenditure variable. Cancer therapies like chemotherapy and surgery are related to major changes in REE [102], and measurements of energy expenditure at a specific point in time may not reflect requirements at other times, making nutritional recommendations for these patients inherently inaccurate, as resting energy expenditure may be higher or lower than expected. Changes in FFM are also not indicative of changes in energy expenditure. Looking at different prediction equations, none seems to have a higher than 70% accuracy [32]. Indirect calorimetry will be more accurate but still carries the aforementioned hindrances. That said, recent studies were sufficiently powered to show that nutritional therapy improves outcomes in cachectic cancer patients, including increased survival rates [99].

12. Other morbidities

Energy estimates in comorbidities tend to err on the higher side [103]. The exercise capacity of frail subjects is not necessarily related to energy expenditure. In this patient population, the Harris-Benedict equations will predict higher energy requirements than the actual numbers, almost certainly leading to overfeeding.

Patients with cystic fibrosis consumed less calories during infectious exacerbations although their requirements were actually elevated. Patients suffering from acute exacerbations of chronic obstructive pulmonary disease consumed fewer calories as well, although energy expenditure was 15% higher. A study on women with chronic obstructive pulmonary disease revealed that predictive equations were inaccurate when compared with indirect calorimetry in this population [104]. The situation is more complex in patients with heart failure, in whom complex interactions exist between metabolic processes are intricate, including reduced oxygen consumption and ATP production [105].Comorbidities, chronic illness and ageing often coexist and promote reductions in BMI and lean body mass. These changes may represent adaptations to the limited metabolic capacity of the circulatory and respiratory systems.

13. The ESPEN approach

Several ESPEN guidelines [78, 95, 98, 106-115] have explored the role of indirect calorimetry in the prescription of patients with various disease states and the salient features are summarized in **Table 5** [1, 2, 13, 20, 32, 39, 78, 87, 95, 98, 101, 106-121].

The scientific approach towards nutritional care requires standardized sets of routines for both assessment and therapy. Indirect calorimetry requires technical and clinical understanding but allows for an actual measurement. Equations are mainly based on patient-related factors such as age, weight and sex, but their “one size fits all” concept can lead to significant errors. When used, the choice of the equation that would fit best is far from trivial, making their use less “complexity-free” than generally considered, while newer indirect calorimetry technologies are reducing the levels of complexity involved with their use.

In the setting of acute illness, best embodied by critical illness in the ICU, the patient population is extremely heterogeneous, making generalizations difficult. Measurements may be complex as well, and due to rapid changes along the phases of critical illness, and the large variability presents a strong case for targeting measured values by indirect calorimetry, and if not available, energy expenditure calculated from oxygen consumption (VO_2) or carbon dioxide production (VCO_2) are preferred over predictive equations [106].

In chronic illness, the aim is to enhance the measurement of the resting metabolic rate in all patients in order to optimize nutritional care. The different alternative approaches to achieve this goal should be considered, according to feasibility aspects. But the objective is more complex than merely the assessment of resting metabolic rate. Physical activity and thermogenesis are two other components of total energy expenditure, and the determinants of total energy expenditure are numerous, including but limited to, FFM and fat mass, age, sex, genetic variables and the effects of hormones and the sympathetic nervous system. Algorithms for the diagnosis of malnutrition are available [58, 59], and should be followed routinely. Malnutrition may manifest as a variety of clinical phenotypes. In an age of the obesity epidemic, the patient with obesity and low muscle mass is becoming more common but is more difficult to diagnose, so particular attention should be paid towards measuring muscle mass. As the world’s population ages, age-related frailty is affecting the lives of many. Frailty is related to weight loss, exhaustion, weakness, slowness and inactivity. These result in high rates of disability, increasing loss of independence and worse patient outcomes. The increases in frailty and obesity with low muscle mass are closely linked, owing to high caloric intake and reduced physical activity. Frailty should be diagnosed on ICU admission or during ICU stay [106], and treatment should be tailored accordingly, avoiding further preventable losses.

ESPEN supports [58, 59] implementation of measurement or assessment of body composition and skeletal muscle mass to optimize nutritional care. Lack of awareness and suboptimal practice should be addressed by education and communication by releasing practical guidelines and making them easily accessible and easy to implement. This is an effort that mandates a partnership between nutrition experts with other healthcare personnel, patients, the general public and the policymakers. ESPEN is concentrating on the dissemination of practical versions of its guidelines, accessible and easy to understand by caregivers and the lay public.

14. Conclusions

The century-old Harris-Benedict equations [1, 2] remain the best available for the prediction of resting energy requirements in healthy, normal-weight individuals. However, those who need nutritional interventions the most, including older people, under- and overweight and those with chronic and acute diseases, are all patients in whom the accuracy of the Harris-Benedict equation is reduced. The Harris-Benedict equations and other predictive equations are widely used in spite of low levels of accuracy ranging from 18% to 70%. Resting energy expenditure cannot be predicted accurately for each individual. Technology for indirect calorimetry continues to advance alongside growing recognition for the importance of assessment of body composition and resulting therapeutic adaptations, although so far technologies for the measurement FFM are far from perfect. FFM remains difficult to measure and variability is high. The best equations should be employed. These include, but are not limited to, the Harris-Benedict [1, 2], WHO [15] and Lazzer equations [19, 21] for patients with BMI below 30 kg/m^2 and the Harris-Benedict [1, 2] and the Mifflin equations for patients with BMI above 30 kg/m^2. Combinations of techniques to assess body composition should be explored to increase accuracy. While indirect calorimetry is becoming more affordable and practical, serving as a gold standard, different models should be compared to ensure accuracy. Gaps in knowledge and practice remain in the different fields of nutritional therapy. These include matters of accuracy and the failure of FFM in improving accuracy of predictive equations. In the field of nutrition, available tools are not many. As technology progresses, we should keep studying them in different scenarios and patient populations, gradually moving away from estimations and guesses towards actual measurements.

Acknowledgements

Funding: This symposium was supported by a grant from the European Society for Clinical Nutrition and Metabolism (ESPEN).

Conflicts of interest:

IB, RB, TC, MC, MdvsS and AL: No conflicts of interest to declare.

DNL: Unrestricted grant from B. Braun and speaker’s honoraria from B. Braun, Baxter Healthcare, Fresenius Kabi and Shire for unrelated work.

EF: Unrestricted grant from Baxter Health, and speaker’s honoraria from B. Braun, Baxter Healthcare, Fresenius Kabi, Nestle, Nutricia, Shire, Lactalis and Aguettant for unrelated work.

MH: Unrestricted grants from Abbott Nutrition and Fresenius Kabi for unrelated work.

CP: Financial support from research grants and unrestricted academic research grants from the public institutions, as well as no-restrictive research grants and consulting fees from the Foundation Nutrition 2000plus, Abbott, Baxter, B. Braun, Cosmed, Fresenius-Kabi, Nestle Medical Nutrition, Novartis, Nutricia-Numico, Pfizer, Shire and Solvay

PS: Unrestricted grant from B. Braun, Baxter Health, Fresenius Kabi, ART Medical and speaker’s honoraria from Abbott, B. Braun, Baxter Healthcare, Fresenius Kabi, Nestle, Nutricia, Cosmed and General Electric.

Author contributions: All authors participated in the Symposium and were involved with the writing of the manuscript, critical revision and final approval.

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Legends for figures

Figure 1: The apparatus used by Benedict [3]. Reproduced with permission from the publishers.

Figure 2: The Harris-Benedict equations as described originally [2]. Reproduced with permission from the publishers.

Figure 3: The accuracy of the Harris-Benedict equation for the estimation of energy expenditure in various patient populations, including under- and overestimations. Data derived from [22, 24, 26, 32-39].

Table 1: Historical landmarks in the study of energy expenditure.

Period/Year	Scientist	Scientific achievement	Comments
18th century	Antoine Lavoisier	Insights into mechanisms of respiration and combustion.	Recognized and named oxygen and hydrogen.
1874	Pierre Paul Broca	First predictive equation for ideal body weight [7]. Coined the term "ideal body weight". Took into account sex differences.	The main concern at the time was the provision of sufficient nutrients to soldiers.
1909	Francis G. Benedict	The development and study of "an apparatus for studying the respiratory exchange" [3].	
1919	J. Arthur Harris and Francis G. Benedict	The publication of "A biometric study of human basal metabolism" [1, 2].	
1929 onwards	Max Kleiber	The construction of respiration chambers research into energy metabolism in animals	Energy "lost" was defined as energy expenditure, in fact a different term for ATP turnover.
1961		The publication of "The Fire of Life" [6], summarizing these studies.	
1951	Alfred Fleisch	The advent of indirect calorimetry, measuring heat production [5].	Heat production is comprised of resting and non-resting energy. Basal energy expenditure was found to decline with age in both men and women.

1959 and 1983	Metropolitan Insurance Life Tables	The Metropolitan formulae describe three body frames and assume health issues accordingly. It should be noted that while height is an important factor, it varies less than weight across populations [8, 9].	Actual body weight showed a 15 kg difference from body weight predicted using height from four different cohorts [10].
1980s	Eric Jequier	Studies into direct calorimetry, measuring heat dissipation, i.e., heat losses by conduction, evaporation, convection and radiation [4].	About 75% of oxidative energy consumption from generated ATP are channeled into heat production, while only 25% is used for work. Energy expenditure comprises of basal metabolism (~73%), thermogenesis (~15%) and physical activity (~12%).

Table 2: The main available methods for the assessment of body composition.

Method name	Principle	What is measured?	Advantages	Disadvantages
Dual Energy X-Ray Absorpiometry (DXA)	X-rays with low- and high-photon energy	Three compartments: -FFM -Fat -Bone	Fast Noninvasive	Irradiation (albeit of a very small amount, 2-5 μSv)
Bioelectrical Impedance Analysis (BIA)	Generally requires surface electrodes, typically on hand and foot Raw electrical data is acquired: -Resistance -Reactance -Phase angle -Impedance	Two compartments: -FFM -Fat	Fast Noninvasive Affordable	Only two compartment (vs. three in DXA)
Air Displacement Plethysmography (ADP)	Whole body densitometry as a hydrostatic weighing method	Two compartments: -FFM -Fat	Fast Noninvasive	Expensive Not available in most centers
Computerized Tomography (CT)	Performed at the level of the 3rd lumbar vertebra	Assessment of fat and muscle areas Two compartments: -Fat -Muscle	Performed in most hospitalized patients for diagnostic purposes	Irradiation (substantial) Applicable only for those in whom it indicated for diagnostic purposes

FFM: fat free mass

Table 3: The advantages and pitfalls of indirect calorimetry and predictive equations

	Indirect Calorimetry	**Predictive Equations**
Accuracy	-High – considered gold standard. -High for both ventilators and canopies. -Up to 20% difference between devices.	Only around 50% accuracy Generally, error around 250 kcal/day, but in large heterogeneous populations with dynamic courses they may be up to 1000 kcal/day!
Cost	Moderate. Between € 14,000 to 30,000 for the device -€ 5,000 yearly for materials and maintenance. -cost of manpower.	None.
Ease of use	-Less Time consuming in the new devices (5 minutes). -Requires experience and a technical understanding. -Require calibrations (less in newer devices).	-Very easily used. -Require little training. -Easily incorporated into electronic medical records.
Availability	-Low 80% of health professionals have no access. -10% have only occasional access. -In settings such as nursing homes or non-western countries access is even lower.	Readily available for clinical use everywhere.
Which parameter?	Resting energy expenditure, VO_2, VCO_2, RQ	Resting energy expenditure but also total energy expenditure.
Tips	-For precise and personalized medicine. -May improve patient outcome. -Should be followed with repeat measurements, optimizing energy balances.	-WHO equation is probably best for patients with BMI <30 kg/m^2. - Harris-Benedict is the equation of choice for BMI ≥30 kg/m^2. -These should NOT be adjusted for over- or underweight.

VO_2: oxygen consumption. VCO_2: carbon dioxide consumption. RQ: respiratory quotient.

Table 4: Examples of diseases that are related to malnutrition, divided according to whether they are of inflammatory or non-inflammatory nature.

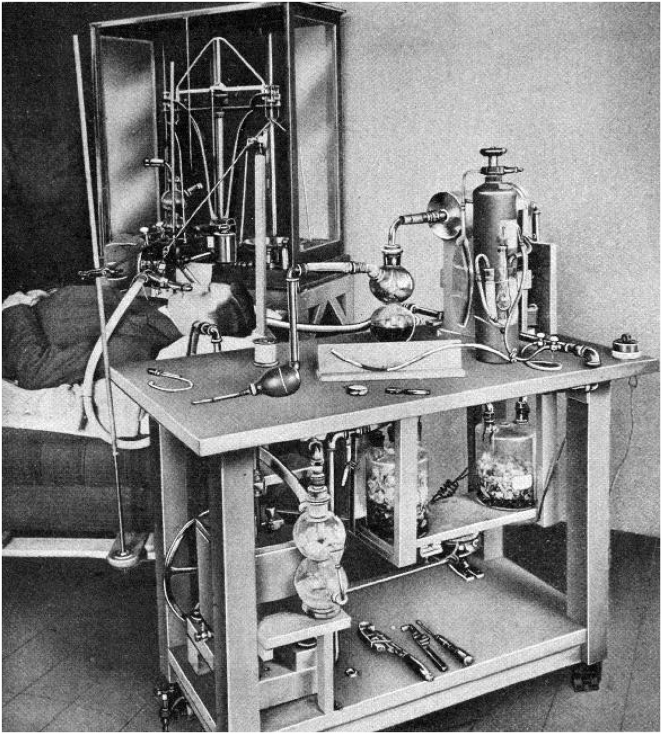
Disease-related malnutrition without inflammation	Disease-related malnutrition with inflammation
Stroke Dementia Parkinson's disease Anorexia nervosa Depression Malabsorption: -Celiac disease -Short bowel syndrome	Cancer Chronic obstructive pulmonary disease Congestive heart failure Infections Trauma Critical illness

Table 5: Energy requirements recommended in various ESPEN guidelines.

Patient population	**Evidence for the role of indirect calorimetry** i.e. should be preferred	**Proposed energy prescription**	**Performance of predictive equations**	**Comments**
Cancer [95]	Yes- REE is high in 40% of cancer patients [101].	The Souza-Ozório-Singer equation [20], using FFM and phase angle, may help improve resting energy expenditure estimation.	Large variation in the performance of predictive equations of REE based on anthropometric parameters [32].	-Adequate nutrition *per se* does not increase tumor growth. - Hypermetabolic patients suffer more from cachexia [116]. - Elevated REE before chemotherapy increased drug toxicity and poor survival.
Surgery [98]	No	Rough estimates of 25-30 kcal/kg/day and protein of 1.5 g/kg/day (using ideal body weight) can be employed.	Surgical patients are highly heterogeneous in both patient and disease parameters and variability is high.	Very limited data.
Critically ill-ICU [106]	Yes (grade B ESPEN recommendation)	Risk of overfeeding during the first days, hypocaloric target of 70% of REE preferred gradually progressing to 80-100% of energy	The large inter-patient variability and the low accuracy of weight-based equations merit careful interpretation.	If indirect calorimetry not available, VO_2 obtained from a pulmonary artery catheter or VCO_2 obtained from the ventilator give a better evaluation of REE than predictive

		expenditure [39].		equations.
Major burns [107]	Yes	The Toronto (adult) [117] and the Schofield (pediatric) [87] equations are advocated.	Protein target should be 1.5-2 g/kg/day for adults and 1.5-3 g/kg/day for children.	
Intestinal failure [108]	Yes	The caloric target should be 25-35 kcal/kg/day.	- Predictive equations perform poorly. - In stable patients on home parenteral nutrition, equations are still inaccurate for most [118], mostly leading to overfeeding.	Individual parameters should be applied, such as disease state and anabolic and catabolic factors.
Polymorbidity [109]	Yes	Weight-based equations?	Very scarce data.	IC should guide nutritional therapy whenever possible (Recommendation grade 0).
Liver disease [110]	Yes	Harris-Benedict and Mifflin equations.	Pooled together, the Harris-Benedict [1, 2] and Mifflin [13] equations probably perform better than FFM-based equations in cirrhotic patients [119].	-Indirect calorimetry is endorsed by ESPEN. -Patients with a sedentary lifestyle should receive 1.3 times REE. - In liver cirrhosis, hypermetabolic patients show better outcomes [120].

Geriatrics [78]	No	30 kcal/kg/day.	Predictive equations generally have about 50% accuracy [121].	Energy Expenditure is generally low, hence the risk of overfeeding may be substantial.
Neurlogical diseases [111]	Yes	30 kcal/kg/day.		Noninvasive ventilation generally reduces REE.
Dementia [112]	No	None available.	No data.	Should provide adequate food intake.
Kidney disease [113]	Yes	The Harris-Benedict equation could be used safely.	A stress factor should not be added, as it could expose the patient to overfeeding.	The ESPEN guidelines currently under preparation.
Pediatrics [114, 115]	No	Schofield (in cystic fibrosis).	Adaptations for age.	ESPEN alongside ESPGHAN recommendations available for cystic fibrosis [114] and pediatric parenteral nutrition [115].

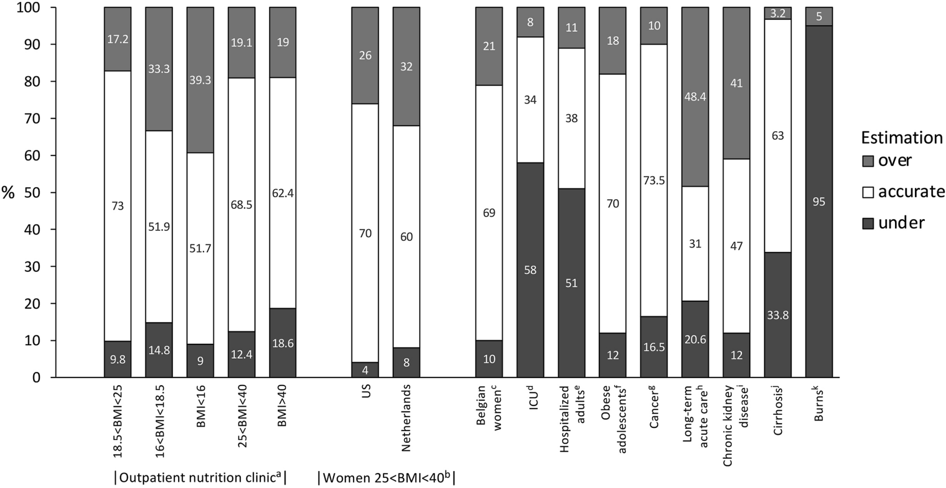


The closest prediction of the daily heat production of a subject can be made by the use of the multiple regression equations,

For men, $h = 66.4730 + 13.7516\, w + 5.0033\, s - 6.7550\, a$

For women, $h = 655.0955 + 9.5634\, w + 1.8496\, s - 4.6756\, a$

where h = total heat production per 24 hours, w = weight in kilograms, s = stature in centimeters, and a = age in years. These equations have been tabulated for values of weight from 25.0 to 124.9 kgm., for stature from 151 to 200 cm., and for age from 21 to 70 years, so that the most probable basal metabolism of an unknown subject may be easily determined.



a Jesus, *et al*. [22] 1726 under-, normal and over-weight patients followed in a nutrition unit
b Weijs, *et al*. [24] 239 US and 208 Dutch overweight and obese women
c Weijs & Vansant [38] 536 normal weight to morbidly obese Belgian women
d Zusman, *et al*. [39] 1440 critically ill patients
e Kruizenga, *et al*. [26] 513 under-, normal and over-weight hospitalized patients
f Hofsteenge, *et al*. [34] 121 obese adolescents
g Purcell, *et al*. [32] 125 patients with cancer
h McClave, *et al*. [36] 213 mechanically ventilated patients in long-term acute care facilities receiving total enteral nutrition
i Kamimura, *et al*. [35] 281 patients with stable chronic kidney disease
j Müller, *et al*. [37] 473 patients with stable, biopsy-proven cirrhosis of the liver
k Dickerson, *et al*. [33] 20 patients with burns of at least 20% body surface area