Clinical Nutrition 38 (2019) 2531–2544

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Indirect calorimetry as point of care testing

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ARTICLE INFO

Article history:
Received 2 June 2018
Accepted 29 December 2018

Keywords:
Indirect calorimetry
Energy expenditure
Hypermetabolism
Nutrition

SUMMARY

Determining energy requirement is a fundamental of nutrition support. Indirect calorimetry (IC) has been long recognized as the gold standard for assessing basal or resting energy expenditure (REE). The measurement of REE is recommended particularly in the situation where adjustment of energy provision is critical. The result of the IC measurement can lead to changes in treatment and since the change can be carried out immediately at the bedside, this may be considered as point-of-care testing. Beyond the nutritional aspects, studies of energy expenditure with IC have brought out more understanding of the metabolic changes during the natural course of diseases or conditions as well as those related to the intervention. The literature in various disease states has shown that changes in energy expenditure may reveal hidden metabolic information that might be translated into clinical information and have the potential of being both prognostic indicators and/or treatment targets.

1. Introduction

Benedict and Carpenter first published their works on respiratory calorimetry in humans in 1910 [1]. This sophisticated system required a large laboratory room. In 1915 Abraham developed respiratory calorimetry as a large closed-circuit chamber created for accurate gas collection. After decades of progress, the devices underwent further development and became the most validated tools for resting energy expenditure (REE) measurements [2]. In more recent times, the development of portable devices has allowed the test to be carried out at the patient's bedside. The measuring process no longer involves the classical ethanol burner calibration or column of spirometry but rather a few simple steps achieved by the push of a button. REE is calculated from the rate of oxygen consumption and carbon dioxide production as proposed by Weir et al., in 1949 [3]. Indirect calorimetry (IC) has been established as the gold standard of energy expenditure assessment across various groups of patients [4–7]. However, this technique is still not widely used. This may be the result of a lack of equipment, scarcity of skilled operators and experienced interpreters, and the relative high cost of IC. Thus, financial and technical limitations appear to be important factors that may impair its generalizable use [8].

As a result of these difficulties, a numbers of REE predictive equations have been developed and are widely used in general practice. However, the studies of predictive equations compared with IC as a benchmark have shown disappointing results in many settings [9–12]. In the critical ill, a systematic review demonstrated that the predictive equations yielded an acceptable estimation for only half of the population while the rest were either over- or underestimated [13]. To date, many leading guidelines still recommend the use of IC, if available, over predictive equations regarding caloric goal setting in nutrition support [5,14].

In addition to becoming a standard REE measurement, the IC studies have provided more understanding regarding metabolic alterations during illness. Generally, the REE increases in relation to the disease severity [15]. Figure 1 illustrates resting energy expenditures in various conditions. Repeated measurement of REE over the course of an illness showed a dynamic pattern which might correspond with disease progression or resolution [16]. Day-to-day variations of REE led researcher to find more precise methods that could capture this change so they could predict REE even more accurately [17]. Body temperature, minute ventilation, cardiac output, etc. were shown to correlate with REE fluctuations and were incorporated into some predictive equations [18–22]. Changes in these dynamic parameters are caused primarily by changes of REE which may represent changes in the “stage” of the disease that cannot be clinically obviously identified [23,24]. Longitudinal measurement of REE during the course of disease may allow us to monitor metabolic changes that occur prior to clinical

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https://doi.org/10.1016/j.clnu.2018.12.035
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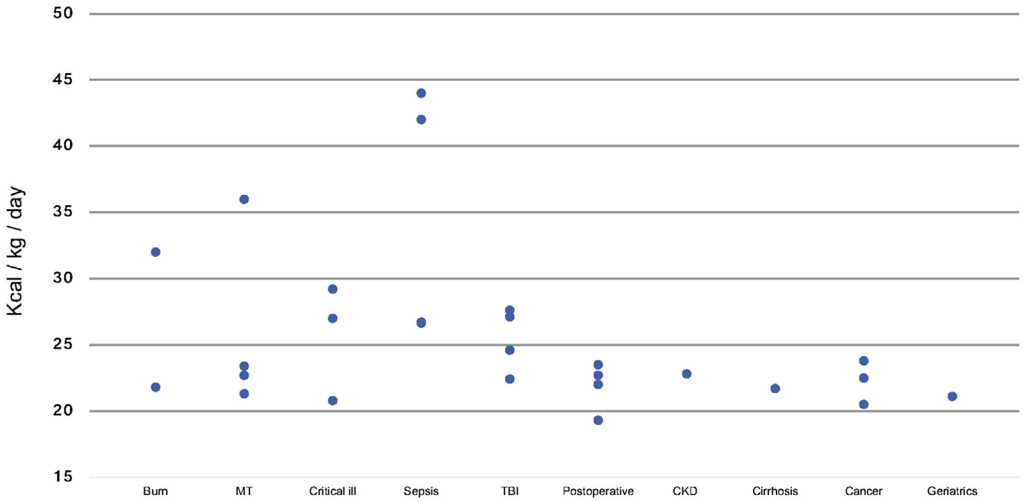

Fig. 1. Measured resting energy expenditure in various conditions including burn [26–33], multiple trauma (MT) [18,26,34–39], critically ill [40–49], sepsis [39,44,50–53], traumatic brain injury (TBI) [35,54–57], postoperative [17,58–62], diabetes mellitus [63–68], cirrhosis [23,69–75], chronic kidney disease (CKD) [76–80], cancer [24,59,81–85], geriatrics [86–89], and home parenteral nutrition patients [90]. Each dot represents the mean of measured REE of each group in the studies. Note that the timing of measurement within each pathological condition may be different between the studies.

improvement or deterioration [25]. In other words, we may be able to anticipate clinical changes or prognosis by "the trend" of REE.

In this review, we describe the use of IC with an example of an application in critical illness as point-of-care testing. In addition, we review the literature studying changes in REE in disease states and discuss how REE measurements may provide more understanding of metabolic change and potentially add clinical values to patient care in both nutritional and beyond-nutritional aspects.

1.1. IC used as point-of care testing to provide energy targets: an example from intensive care

An important element of the practice of medicine is problem-solving. Point of Care Testing (POCT) is defined as medical diagnostic testing outside the clinical laboratory and in close proximity to where the patient is receiving care. The driving notion behind POCT is to bring the test conveniently and immediately to the patient. Examples of POCTs which have been incorporated into routine standard of care include arterial blood gas analysis which detects hypoxemia or hypercapnia and glucometer used to monitor blood glucose levels. These tests provide results which can affect treatment decisions within minutes at the bedside.

While using the same principles from the past, advanced technology has resulted in the feasibility of IC measurements in daily practice. Recently, devices have been developed which minimize the complicated calibrating process, the cleaning burdens, the delay in obtaining results, and in the cost of IC [91–93]. Today IC is available in an on-the-go handheld size, either as a stand-alone device or as an extended part of mechanical ventilator. The measurement can be performed at the bedside for in-patients, or in the clinic for out-patients. Result can be obtained immediately in order to guide physicians on nutritional management particularly in situations where the caloric prescription needs to be strictly adjusted and controlled, for example in critically ill patients. The effects of under- and overfeeding in this population have been well established. Negative energy balance in the critically ill setting was shown to lead to negative nitrogen [94] and protein balance [95], increase of infectious complications [96,97], wound disruption, prolonged mechanical ventilation [98], hospitalization [99], as well as mortality [100]. Likewise, overfeeding may result in respiratory compromise or weaning failure, multiple metabolic derangements, hepatic dysfunction, volume overload, and azotemia [101–103]. The results from the measurement should therefore be used to guide energy prescription. Current evidence suggests that lowest mortality in critically ill patients was achieved when calories were delivered at 70% of REE [43]. This justifies the inclusion of IC measurements into routine practice a POCT.

Data from observational studies have shown that receiving energy closer to the measured target correlated with fewer infectious complications [96,99] and lower mortality [43,100]. To our knowledge, there are 4 randomized trials which addressed clinical outcomes of the provision of energy according to the measurement. The TICACOS study in critically ill patients showed that using an IC-directed nutritional goal yielded higher energy and protein delivery than when guided by predictive equations (2,086) ± 460 vs. 1480 ± 356 kcal/day in the control group, $p = 0.01$ and 76 ± 16 vs. 53 ± 16 g/day, $p = 0.01$ respectively) with a trend to lower mortality in the intention-to-treat analysis (32.3% in study group vs. 47.7% in the control group, $p = 0.058$) [45]. Heidegger et al. demonstrated a reduction of nosocomial infections by using supplemental parenteral nutrition to achieve caloric target driven by IC [104]. A similar finding was reproduced in another study by Sirak et al. [97]. A recent randomized controlled trial which compared individualized goal-directed nutrition therapy guided by IC and 24 h urinary urea with a weight-base predictive equation according to European Society for Clinical Nutrition and Metabolism (ESPEN) in ICU patients showed no difference between the two groups regarding various clinical outcomes (mortality, rate of organ failure, infection complications, length of stay, and physical quality of life assessed by SF-36) [46]. A possible explanation is the amount of calorie and protein provision in the two groups of the latter study were too close to each other and might represent two opposite ends of an "optimal zone" proposed by Zusman 's study. These authors illustrated an U-shaped curve correlation between the percent of calories delivered over measured energy expenditure (mREE) and mortality in ICU patients where an apparent mortality lowering effect was seen when energy was delivered in the range of 50–90% REE and possibly considered optimal [43].

Benefits of IC-guided nutrition therapy are also evident in other settings. Anbar et al. conducted a study in elderly patients with hip fractures and showed a significant reduction in total postoperative complications in the group which received nutrition support

guided by repeated REE measurement as compared to routine nutritional care (27.3% vs. 64.3% respectively, p = 0.012) which was due mainly to a reduction in infectious complications [88]. A small preliminary study showed that caloric adjustment to keep measured RQ > 0.83 in traumatic brain injury reduced the degree of negative nitrogen balance caused by fixed amounts of calories provided according to the Harris Benedict equation [105].

1.2. Changes of REE and their clinical correlations in disease states

1.2.1. Acute illness

In the past, metabolic changes in critically ill patients were proposed to be divided into 2 phases, the ebb and flow phase of Cuthbertson et al. [106] (Fig. 2). The ebb phase was characterized by a decrease in metabolism which occurred immediately after the onset of disease or injury. The flow phase followed after 24–48 h with a hypermetabolic period whose severity was considered to correspond with the severity of injury. The studies of longitudinal changes of REE in critically ill patients in this era were found to support the concept of metabolic changes during severe stress. Most of these studies described an increase in REE during the first 4–7 days of study, reaching a peak during the second week, followed by a gradual decline [107,108]. An increase in REE during the first few days was proposed to be the result of diet-induced thermogenesis as well as an evidence of a flow phase [107].

In addition to disease factors, modalities of treatment and interventions may also influence REE in critically ill patients. Frankenfield et al. depicted a rather steady pattern of REE change over time in small groups of critically ill patients [34]. Zusman et al. conducted a large retrospective study that showed no specific pattern of REE over time from data of more than 5000 IC measurements in 1375 ICU patients [43] (Fig. 3). The lack of a recognizable pattern of REE could have many explanations. Early nutritional intervention which is recommended by many guidelines and practiced worldwide has brought about an increase in energy expenditure due to feeding and hence has driven the REE during the early period and may attenuate the inflammatory response in the late phase. Many interventions and treatments also affect REE, for example, positive pressure ventilation aids in breathing and may therefore decrease the metabolic demand.

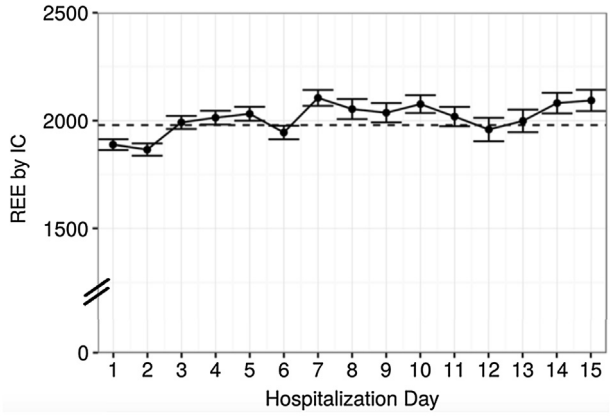

Fig. 3. Mean REE of critically ill patients by hospitalization day (Adapted with permission from [43]).

Sedation, paralyzing agents, therapeutic hypothermia all cause a reduction in VO_2 and energy expenditure [35], blunting the rising REE usually seen in the past. Therefore the changes of REE do not only reflect the natural course of disease but also the summation of metabolic disarrays caused by concerted mediators from neuroendocrine, autonomic nervous system, and immune systems that interact with disease as well as medical interventions. However, there is also another possible explanation that should be borne in mind. Due to the very large pool of data in the Zusman study, variations of REE may be misleading. Significant individual day-to-day variation may exist despite the fact that no difference in mean REE was detected [17].

The degree of increase from normal REE may reflect the severity of the metabolic response to insult. REE was shown to correlate with CRP at single time points [48] but they lost their association during the course of illness [107]. One study in children failed to showed a correlation between REE and nutritional status according to anthropometric measurements [109]. To our knowledge, there is no study assessing the prognostic value of REE in general critically ill patients.

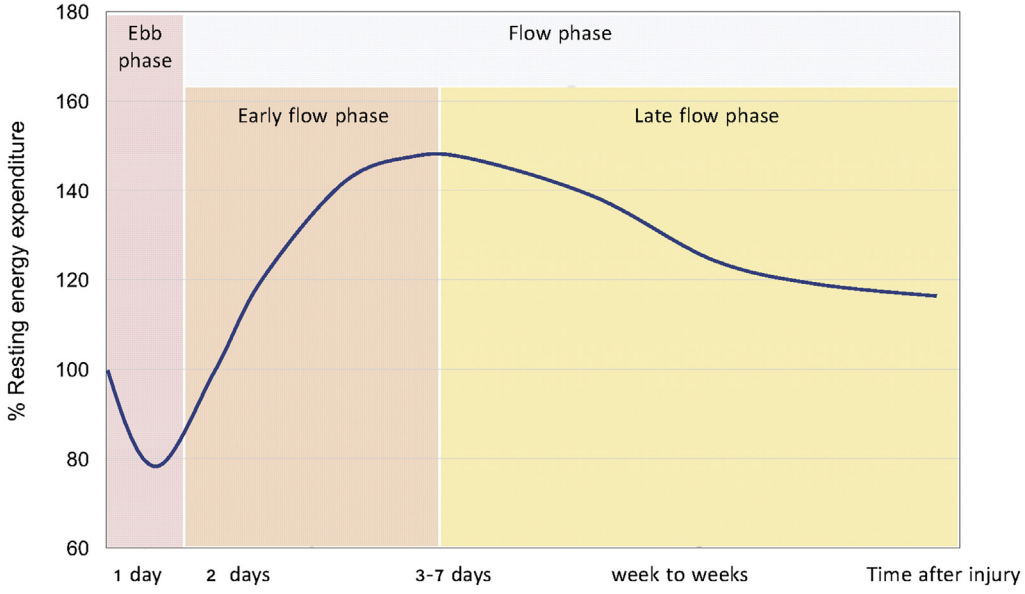

Fig. 2. Ebb and flow phases to represent the metabolic response to injury proposed by Cuthbertson et al.

1.2.2. Sepsis

Sepsis is characterized by a hyperdynamic cardiovascular response against infection. However, the tissue oxygen consumption may not increase to the same degree of the increase of cardiac output because the microcirculatory oxygen extraction is disturbed by bacterial endo- and exotoxin [110,111]. Oxygen consumption (VO_2) and REE even showed a decrease when the severity of sepsis increases. Kreymann et al. reported a significant difference in VO_2 and REE between patients with uncomplicated sepsis, sepsis syndrome, and septic shock (mean VO_2 180 ± 19, 156 ± 22, 120 ± 27 ml/min/m^2, mean REE +55 ± 14%, +24 ± 12%, and +2 ± 24% from predictive REE respectively). This study also noted that the group with uncomplicated sepsis and sepsis syndrome had a lower mortality than the septic shock group and proposed that the hypermetabolism stage might reflect the patient reserve to express an adequate response to infection [16]. As study in sepsis children observed that the lower the REE, the poorer was the outcome and the extremely low REE patient quickly deteriorated and died [112,113]. On the contrary, a recent observational prospective study in severe sepsis adult patients by Wu el at showed that survivors had significantly lower REE as compared to non-survivors (measured REE to predicted REE ratio, mREE/pREE, 1.3 ± 0.6 and 1.8 ± 0.4, $p = 0.003$) and the higher mREE/pREE ratio was associated with a higher mortality (OR 1.018, 95% CI, 1.010–2.544, $p = 0.031$) [114]. These opposite findings may have many possible explanations. First, it should be noted that these 2 studies were conducted 22 years apart so the differences in clinical practices and their influences on REE may be substantial and should be borne in mind. Second, it is possible that the appropriate body response to each degree of sepsis is different. While hypermetabolism is considered appropriate in an uncomplicated course, it may reflect failure to step down metabolism to cope with poor tissue perfusion in severe sepsis and septic shock. All participants in Wu's study received vasoactive agents so they are comparable to the septic shock group in the Kreymann study. The non-survivor group in the Wu et al. study may exhibit an excessively high REE, or fail to adapt, during septic shock hence explaining their poor outcome. Another possible cause is that these studies captured their REE at different time points. REE during recovery from sepsis was shown to increase more than that measured during sepsis [112]. While Wu et al. measured REE daily in the first 5 days after admission, therefore representing the initial phase of sepsis, Kreymann et al. analysed 76 measurements from 30 septic patients during their ICU stay which ranged from 1 to 22 days. Uncomplicated groups might represent the recovery phase of sepsis while the period of sepsis had occurred prior to the measurement so that the higher REE patients tended to have better outcomes. The study of Kreymann collected only the lowest VO_2 value from each patient in every stage for analysis so it might not truly represent the mean REE in septic patients. Furthermore, the study was not designed to detect differences in mortality regarding differing REEs. It is predictable that septic shock patients should exhibit higher mortality than those with uncomplicated sepsis regardless of REE. Further study should emphasize how specific host (e.g. well-nourished or malnourished) factors affect each severity stage and period of sepsis as well as any association with patient outcome. This will give more understanding of the metabolic evolution during sepsis and possible prognostic value of REE in this group of patients.

1.2.3. Multiple trauma

Skeletal trauma results in metabolic changes to the body. Studies of REE in multiple trauma patients showed a hypermetabolic state after injury with wide individual variation [50]. Sedation, neuromuscular blocking agents and mechanical ventilation were reported to decrease REE, however the severity of injury overwhelms their effects so that patients usually exhibit increases in REE despite these interventions [36,50]. Controversy existed regarding the correlation between the degree of hypermetabolism and severity of injury. The Injury Severity Score (ISS) is the most common score used in these studies as it has been shown to have a good correlation with morbidity and mortality [115]. The ISS is calculated by the summation of the square of the 3 highest scores obtained from 6 body regions where each region is weighted equally in the score. From a metabolic point of view, differences in the of metabolic burden of the same level of injury in different regions could be substantial. Abdominal injury with visceral organ involvement could cause a more pronounced hypermetabolic response than the fracture of extremities. This may explain the discordant study results.

To the best of our knowledge, only 2 studies using IC-guided caloric prescription in multiple trauma patients have been performed. Frankenfield et al. conducted a prospective trial which divided patients into 3 groups who received different amounts of calories (mainly by variation of calorie from fat) given parenterally. The three group received roughly 1.25, 1.0, and 0.75 mREE for 4 days, respectively. The groups who received 1.25 and 1.0 of mREE exhibited the deposition of fat. No differences in the degree of protein loss, nitrogen balance, or serum prealbumin were found among the 3 groups. The authors concluded that a hypocaloric practice did not havea negative effect on protein catabolism or synthesis in trauma patients and might be used to avoid the over-prescription of carbohydrate and fat which may result in overfeeding [116]. Another prospective study was performed with the intention to prove the effects of olive oil in trauma patients. By the end of the study, IC showed comparable REE between the groups. The intervention group who received olive oil-based nutrition was unintentionally fed with lower calories than the control group (17.9 kcal/kg vs. 22.3 kcal/kg, $p = 0.03$). The intervention group showed a significantly lower blood glucose, CO_2 production, minute ventilation, shorter mechanical ventilation duration and ICU stay. Despite insignificant differences of monocytic HLA-DR expression (as a marker of immune function in this study) between the groups, a lower infection complication rate was observed in the intervention group. They proposed that the benefits seen in the study group might partly be caused by hypocaloric feeding as well as a lower glucose load in the parenteral regimen in the intervention group [117].

1.2.4. Postoperative phase

Surgical procedures can be considered "iatrogenic injury or trauma" from the metabolic point of view. Oxygen consumption is increased by the injured tissue hence resulting in an increased REE. However, the increase from surgical injury is lower than that seen in sepsis and trauma. Pre- and postoperative studies of REE observed only modest increases in REE during the early postoperative period. An average of 7–10% increment from baseline REE or from those with matched controls have been reported [58,59]. An uncomplicated course of surgery further decreases the difference between pre- and postoperative REE. Fredrix et al. reported only a 3% increase of REE after uncomplicated abdominal surgery [59]. Though only a minor increase in postoperative REE was shown, 30% of postoperative patients exhibited a hypermetabolic state particularly those with a complicated postoperative course [59]. The majority of patients experienced weight loss after surgery. Non-protein respiratory quotient (nPRQ) and urinary nitrogen study demonstrated that this loss was mainly from fat rather than body protein [15]. Conventional perioperative fasting and delayed initiation of oral intake probably further aggravates weight loss.

Modern perioperative management encompasses multimodalities to attenuate the surgery-induced stress and inflammation. Minimal invasive surgery has become a standard technique in

many surgical procedures. This helps to limit the extent of tissue injury, reduce blood loss, and even shows metabolic benefits. Yatabe et al. found that the average of postoperative REE of patients underwent laparoscopic esophagectomy was 18 kcal/kg, in other words 83% of that predicted by HB [60]. The hypometabolic state was postulated to be caused by the less invasive surgical technique which limits tissue injury and the practice of sedation and ventilation in the ICU. Together with postoperative early enteral nutrition, this hypometabolic state would allow patients to have better perioperative energy balance and may be translated to the more rapid recovery seen following minimally invasive surgery.

1.2.5. Traumatic brain injury

Dating back to 1975, hypermetabolism in traumatic brain injury (TBI) has been well documented. REE in TBI can vary widely in both degree and duration. Data from a systematic review showed that the mean REE in TBI patients measured by IC ranged from 87% to 200% of the predicted value at some point during the first 30 days after the insult. Changes in metabolic rate were proposed to be caused by the overwhelming release of inflammatory cytokines and mediators following injury [118]. In the present, multimodality treatments incorporated into current standard practice have impacts on metabolism. Sedatives, neuromuscular blockade, controlled normothermia, therapeutic hypothermia, and the use of beta-adrenergic blockers all have an effect on reducing REE in TBI. Hence the pattern of energy expenditure in TBI has changed significantly. Many predictive equations of REE have been proved to inaccurately estimate energy expenditure in this population [57,119].

There is very little data regarding non-nutritional application of IC in TBI patients. A decrease in cerebral oxygen demand is desirable in the treatment of TBI to limit neuronal damage. Hypothermia is applied to reduce oxygen utilization by the brain, and alsoto decrease overall oxygen consumption, due not only to its neuroprotective effect but also to a reduction of intracranial pressure, and enhanced cerebral blood flow to meet oxygen demand. However, a too low oxygen consumption in TBI may reflect failure of the traumatized brain to utilize oxygen, in other words, the process of dying neuronal tissue. An abnormal reduction of oxygen consumption to <170 ml/min/m^2 in response to hypothermia in TBI is probably a marker of an unfavorable outcome [120]. Bitzani et al. demonstrated significant reduction of REE to the point of 25% lower than basal metabolic rate in TBI patients with brain death and those who later progressed to brain death [121]. This finding may be partly explained by reduced cerebral oxygen consumption as well as the effect of hypothermia. To our knowledge, there is no literature studying outcome of TBI patients regarding varying REEs.

1.2.6. Burns

A new era of intensive burn care has brought various strategies to accelerate recovery, and to reduce morbidity and mortality. Introduction of these modalities has changed the face of postburn metabolic response. Nowadays, the magnitude of hypermetabolism in burns is dampened. Well-known REE predictive equations from the past are no longer valid, with a trend to overestimation [28,122]. Though many newly developed predictive equations with better precision and accuracy, more suitable for modern burn care, have been introduced, REE measurement is still recommended as the gold standard to determine patient requirements.

Postburn hypermetabolism is unique in its severity and duration and possesses the first rank in magnitude of increases in REE among groups of trauma patients. This increase may be as high as 100% above normal [29,123]. A forceful catabolic drive from endogenous catecholamines and numerous inflammatory cytokines has been regarded as underlying this finding [124,125]. The hypercatabolic state leads to glycogen, fat, and skeletal muscle breakdown. An increase of hepatic gluconeogenesis provides more glucose in order to meet the increasing demand by injured tissues. Though this hypermetabolic state is an appropriate initial response to burn trauma, its persistence has devastating effects. Prolonged hyperglycemia will increase the risk of infection. Continuous utilization of amino acids under the influence of inflammation would not allow the anabolic phase, as well as healing process, to intervene. Progressive catabolism results in malnutrition, delayed wound healing, immune suppression, poor physical recovery, and subsequent death.

Decreasing the degree of hypermetabolism in burns may be considered as another target of treatment. Attenuation may limit the catabolic injury while promoting an anabolic environment for recovery at the same time. Complete burn wound excision with full-thickness grafting has been reported to temporarily lower VO_2 to pre-burn baseline while partial burn excision with full-thickness graft did not [126]. REE also demonstrated a decrease after extensive excision of infected burn wounds as compared to the preoperative state [127]. Adequate surgical removal of burnt or infected tissue helps to decrease the inflammatory process induced by injured tissue. Many studies have shown benefits of early burn wound management and wound closure on mortality. Temperature control and a humidified environment can offset the hypermetabolism induced by thermogenesis to combat heat loss [128,129]. Pain control and sedation alleviate physical agitation which may result in decreased energy demands. Beta-adrenergic blockade and anabolic steroids are also proven to attenuate the hypermetabolic response and improve outcome [125].

Though many strategies have been introduced to lessen the degree of hypermetabolism, it should be expected to persist in some degree throughout the hospital course and healing period. The peak of REE in thermal injury may be seen at a mean of 7–10 days after the burn in moderate to severe burns (TBSA 30–70%), or as late as 21–45 days in case of extremely severe burns (TBSA>70%) [130]. Milner et al. reported the time to return to baseline REE at 100–150 days postburn in 20–40% TBSA and 250 days postburn in those with >70% TBSA [131]. It may be observed up to 12 months after injury or 6 months after complete healing of severe burns [132]. A too early decline of REE to hypometabolic state may be considered as portending a bad prognosis. A large prospective study in burned children found that a decreasing REE during the first 6 weeks of admission was strongly correlated with mortality. In this study, non-survivors seemed to have a lower REE than survivors but the difference did not reach statistical significance [133]. On the contrary, persist hypermetabolism during the hospital course was found in the more complicated cases with more frequent septic complications and multiple organ failure and consequent higher mortality [134]. Whether the magnitude and/or direction of metabolic change infers any prognostic value on mortality is controversial. Inconsistent results may be explained by different definitions of hyper- and hypometabolism among the studies. The time point of IC measurement may also influence the results and should be taken into account.

1.2.7. Malignancy

A hypermetabolic state with an increase in energy expenditure in cancer patients has been noted while their calorie intake was not found to increase [135]. Thus more frequent negative energy balance and weight loss were reported in this group as compared to those with normo- or hypometabolism. A significantly higher mREE per kg of lean body mass has been reported. This finding confirms that the increase of REE is not only a result of different lean body mass. The hypermetabolic group showed lower performance status and experienced more frequent therapy-related

toxicity [83,84]. While cancer treatment was shown to double survival time as compared to supportive care in overall patients, the prolonging survival effect seems to be blunted in the hypermetabolic subgroup. Vazielle et al. found that hypermetabolic metastatic cancer patients had decreased survival during cancer treatment compared with the normometabolic group (14.6 vs. 21.4 months respectively, OR: 1.48; 95% CI: 1.01, 2.17; P = 0.044) (Fig. 3) [84]. Bosaeus et al. reported a decrease in survival in cancer patients who exhibited hypermetabolism in the palliative setting [135]. A possible explanation for the adverse effects of hypermetabolism on cancer outcome is that a high REE reflects a higher degree of inflammation and metabolic burden caused by malignancy. Hypermetabolism was found to have correlation with higher systemic inflammatory markers [83]. Some studies showed a positive correlation between REE and tumor size [136] and tumor metabolic activity detected by 2-deoxy-2-[18F]fluoro-D-glucose uptake on positron emission tomography [24]. Increased Cori cycle activity, hepatic gluconeogenesis by using lactate as substrate pathways to produce ATP, and Warburg effect, upregulation of glycolysis which tumor cells convert glucose to lactate anaerobically for ATP despite the presence of oxygen, were evidenced in many studies and also proposed to play roles in the hypermetabolic state [137–140]. The mathematical model proposed by Friesen et al. has shown that it could cost a person an additional 100–1400 kcal/day to host a tumor [141]. When patients fail to increase their energy intake to meet the demands, loss of body cell mass occurs. However, in the presence of inflammation, REE can remain increased despite the decrease in lean body mass. Many studies have demonstrated hypermetabolism detected in cancer patients regardless of their weight and body composition [142,143]. A proportion of patients with hypermetabolism was even higher in the low body mass index (BMI) group as compare to those with normal to high BMI [144]. Failure to downregulate metabolism during loss of lean mass further worsens their condition. This process has been described as cancer cachexia which eventually leads to a poor clinical outcome.

On the other hand, hypometabolic presentations in cancer patients are poorly understood. This has been reported with a prevalence around 10–20% of patients with solid tumors. Most studies defined hypometabolism by comparing mREE to pREE using the Harris Benedict equation. Using weight-based calculation of REE might result in overestimation of those with less lean body mass, especially in sarcopenic obesity, so that the ratio of mREE/pREE was underestimated and interpreted as hypometabolism. However, some studies observed a decrease in REE in kcal per kg of lean body mass. This finding supports the fact that other factors also contribute to changes of the REE e.g. type, location, and size of tumor, presence of liver metastasis.

Studies in cancer patients have revealed that the hypometabolic subgroup exhibit less frequent negative energy balance, weight loss and a lesser degree of inflammatory markers as compared to those with hypermetabolism. A better prognosis of the hypometabolic patients with longer median survival time was observed when compared to the hypermetabolic group but somewhat similar to the normometabolic group which had the best survival (Fig. 4) [83,84,135]. It was also postulated that hypometabolism may reflect a physiologic adaptation to chronic low energy intake as a protective mechanism to preserve body mass [135]. A lesser degree of inflammation may allow the body to maintain function and hence lead to a better prognosis. On the contrary, a small trial documented that hypometabolism lung cancer patients had a shorter mean disease-free survival than those with a hypermetabolic state. However they defined hypometabolic patients by comparing patient mREE to matched controls [85].

Many pharmacologic treatments with the aim of modifying metabolism in cancer patients are promising. Data from a systematic review showed that omega-3 polyunsaturated fatty acid supplementation in pancreatic cancer patients resulted in a significant decrease in REE, increase in body weight and improved survival [145]. Assessment of energy expenditure by IC may allow better selection of patients who are most likely to have benefit from metabolic modification or guide dosage adjustment over the course of the disease (for example, hypermetabolic patient may benefit from propranolol rather than those with hypometabolic, or the drug should be withhold temporarily during transient hypometabolic episode after radiotherapy and may be resumed once hypermetabolism rebounds). Re-normalization of REE may be set as another goal for nutritional therapy. To endorse this, investigations should emphasize more the selection of patients (regarding type of malignancy, stage of disease, nutritional status, and metabolic pattern identified by IC, etc.). The concept of personalized medicine should be highlighted in the future.

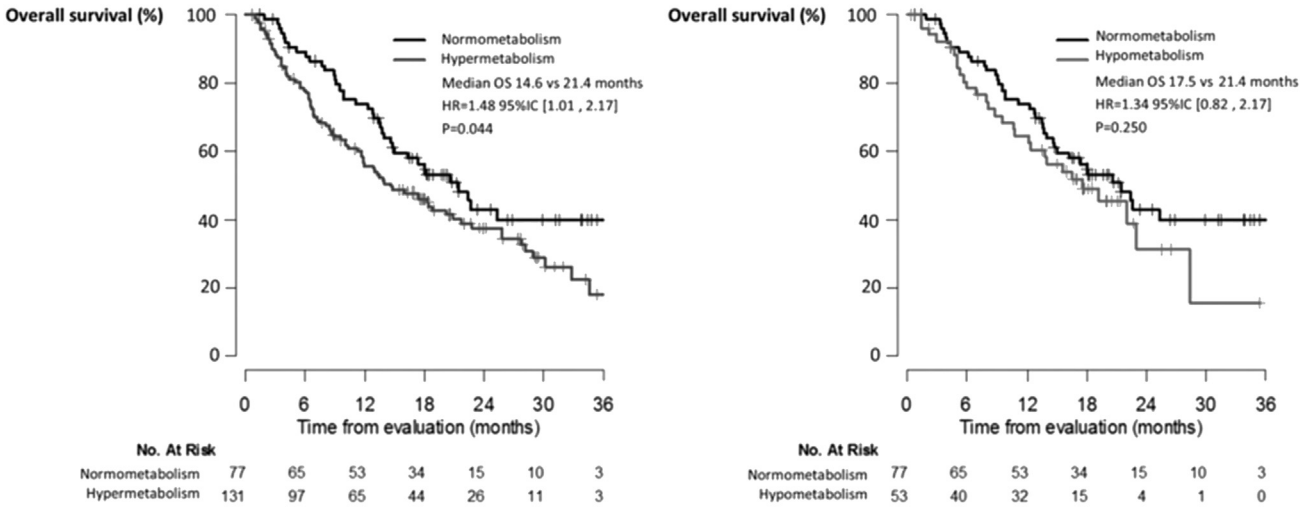

Fig. 4. Cox model comparing overall survival in metastatic cancer patients according to metabolic status (Reprinted with permission from [84]).

1.2.8. Cirrhosis

The liver is the major site of metabolisms of 3 macronutrients, carbohydrate, protein, and fat. As liver function declines, metabolic changes in nutrient utilization may be anticipated. The Respiratory quotient (RQ) changes according to the main substrates which are being metabolized. The RQ of fat, protein, and carbohydrate oxidation is 0.7, 0.82, and 1.0 respectively. The measurement of RQ may imply which energy substrates are being utilized proportionally. Liver glycogen storage decreases in cirrhosis and easmay become depleted, resulting in more fat and protein mobilization and utilization as energy substrates. Therefore, the more the RQ approach 0.7, the more hepatic deterioration is implied as it reflects poor hepatic glycogen synthesis and reservoir. Many studies have showna correlation between the decrease of non-protein respiratory quotient (npRQ) toward 0.7 and the progression of cirrhosis [146,147]. An observational study in liver cirrhosis patients showed that patients with npRQ $\geq$0.85 had significantly better survival than those whose npRQ <0.85 [70,148]. Significant improvement in npRQ by late evening snack intervention in cirrhosis patients [149–151] and liver transplantation [152] have been reported. In clinical practice, npRQ may be used as one of the parameter reflecting progression of cirrhosis, as well as a surrogate marker of the adequacy of replenishment of hepatic glycogen reservoir by for example, a late evening meal.

In general, energy expenditure in cirrhosis is considered comparable to that of normal [153]. However, a hypermetabolic state in cirrhosis is not uncommon and has been reported with a prevalence ranging from 5 to 34%. Neither clinical nor laboratory tests appears to identify this hypermetabolic state in cirrhosis so it may only be detected by calorimetry [69,154,155]. Worsening of hepatic function with an inability to remove catecholamine from the circulation was proposed to underlie hypermetabolism as studies showed elevation of serum catecholamine levels in cirrhotic patients with an increased REE [75]. The hypermetabolic state in cirrhosis showed correlation with prognosis in many studies. It was related to a lower survival rate as compared to normo-metabolic patients with viral cirrhosis [70]. Mathur et al. reported shorter transplant-free survival (patients were censored when dead or underwent transplantation) in hypermetabolic cirrhotic patients as compared with non-hypermetabolic patients (9.7 versus 31.8 months, P = 0.05), however criteria for liver transplantation were not clearly defined in this study [71]. Preoperative hypermetabolic cirrhotic patients also showed a trend of lower survival after liver transplantation than those with normo- and hypometabolism [72]. A recent prospective trial in Brazil showed that cirrhotic patients with a REE $\geq$1190 kcal had significant higher survival than those with REE <1190 (Fig. 5) [73]. As the appendicular skeletal muscle mass index did not correlate with REE in this study, it was less likely that the longer survival in the higher REE group could be explained by better nutritional status. At a glance, this finding seemed to oppose the aforementioned studies; however this study analyzed survival by crude REE while the others compared patients according to the ratio between their mREE against their predictive ones (mREE/pREE). The group with REE $\geq$1190 kcal in the Brazilian study does not represent hypermetabolic cirrhosis patients as the higher REE does not mean a high mREE/pREE, particularly when weight-based REE equations were used as a predictive method. Fluid accumulation in cirrhosis can simply result in a higher pREE and hence low mREE/pREE. Besides, a cut point of <1190 kcal in this study might be considered extremely low as the mean mREE in the study was 1620 kcal/day. Taken together these findings, do not support the prognostic value of mREE in cirrhosis at this time but a U-shaped curve of relationship between mREE and prognosis might be hypothesized.

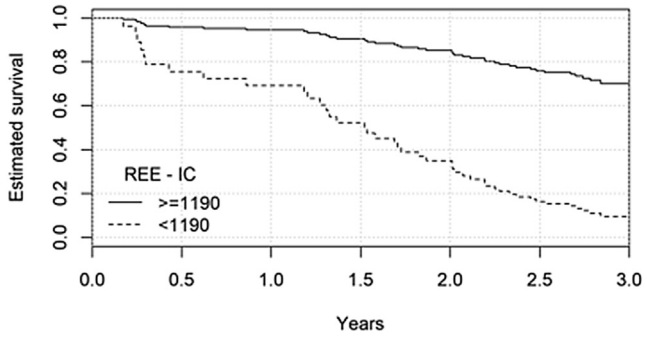

Fig. 5. Comparison of estimated survival in cirrhosis patients according to measured REE (Reprinted with permission from [73]).

Beta-blockers are commonly used to prevent varices in cirrhotic patients with portal hypertension. Its effects on metabolism and nutrition theoretically may be considered as a nutrition intervention for hypermetabolic or malnourished cirrhosis patients. Beta-blocker infusion in stable cirrhotic patients was shown to reduce energy expenditure by 5% [155], however its effect was not reproduced in a small cross-over randomized trial giving oral nadolol to stable cirrhotic patients [156]. The latter study failed to recruit hypermetabolic patients into the study (1 hypermetabolic patients out of 22 subjects) and intentionally excluded malnourished patients to whom benefits of REE-reduction intervention may be more pronounced. IC may help to select hypermetabolic cirrhotic patients who should receive beta-adrenergic blockade therapy in addition to those indicated due to portal hypertension. Whether beta-blocker dosage adjustment according to REE in this group of patients would benefit needs to be explored.

1.2.9. Renal failure

As the kidneys are one of the most metabolically active organs that contribute to REE, a decline in kidney function which results in lower renal oxygen consumption should lead to a decrease in REE. However, studies of REE in chronic kidney disease (CKD) patients have had diverse results. Some studies demonstrated that REE in CKD patients was equal to or lower than those of matched healthy controls independently of lean body mass [157–160]. Panesar et al. showed that REE in CKD patients decreased as renal function deteriorated. It might reflect a reduction of renal energy expenditure as well as metabolic adaptation to a decrease in energy intake which showed a correlation with REE in this study [161]. Conversely, one study reported a higher REE in end stage renal disease as compared to predicted REE [162]. REE was shown to increase with uremic toxic generation [163]. Avesani et al. reported neither correlation between REE and serum creatinine nor creatinine clearance in CKD patients [164].

Renal replacement therapy also effects REE in CKD patients. Both peritoneal dialysis and hemodialysis patient were shown to have higher REE than predicted REE [162] and more than those of healthy subjects. Furthermore, each hemodialysis session was demonstrated to increase REE in dialysis-dependent patients [165]. However, these are not universal findings. Kamimura et al. observed comparable REE between those patients on hemodialysis and healthy controls even after adjustment by fat-free mass (FFM) [166]. Another study found similar result but they used calculated REE instead of mREE [167]. On the other hand, Kogirima et al. found a lower REE in hemodialysis patients compared with healthy normal controls which might be caused by poor nutritional status [168].

Inflammation appears to be an important determinant of REE in CKD patients. Many studies found that higher c-reactive protein (CRP) level correlated with increased REE [164,166,167,169]. An increase in REE along with CRP was shown to be associated with loss of lean body mass, malnutrition and even increased mortality and cardiovascular death in peritoneal dialysis patients [169]. High inflammatory markers found in CKD patients may represent subclinical inflammation from uremic toxins themselves, concomitant diseases (e.g. diabetes mellitus, hyperparathyroidism), previous episodes of volume overload, or concealed infections [80,170]. Utaka et al. observed a significant reduction of REE accompanied by a decrease in CRP after infection was treated in CKD patients [171]. These findings emphasize the relationship between inflammation and REE in chronic diseases and potential treatable target to modify REE. Discordant results among many studies regarding REE in CKD and those with renal replacement may partly be explained in addition to difference in methodology, by variations of the inflammatory status and comorbidities of participants which had not been adequately taken into account.

On the contrary, acute kidney injury (AKI) has not been shown to affect REE. Concomitant conditions, such as sepsis, mostly play role in the hypermetabolism found in AKI patients [160]. In contrast to ERSD, effects of renal replacement therapy on REE in AKI is vague. Studies using IC failed to detect differences in REE between AKI patient with and without renal replacement therapy, whether the measurements were conducted in the interdialytic interval [47,172] or during dialysis sessions [173]. Validation studies showed low precision and accuracy of many predictive equations in predicting REE in AKI patients and hence emphasize the need for REE measurements [47,174]. Only one study showed benefit of IC-directed calorie delivery in AKI. Scheinkestel et al. conducted a prospective study to demonstrate the effect of different amounts of protein delivered to critically ill patients with AKI requiring continuous renal replacement therapy. Caloric prescription in this study was directed by IC measurement in nearly 70% of patients and its result showed that mortality in this study was lower “than predicted”. However, there was no control group regarding caloric prescription in the study [175].

1.2.10. Obesity

To find an effective weight management strategy becomes one of the most challenging tasks for researchers as the prevalence of obesity increases worldwide. The key to success may lie with an understanding of energy balance. REE was found to decrease in varying degrees during weight loss. Change in energy expenditure during weight reduction was studied extensively and the reasons for this change were found to relate closely with the change of body composition. Fat mass (FM) is generally considered as metabolically inactive tissue and contributes less to the REE than fat-free mass (FFM) which is more metabolically active. However, the high percentage of body fat in severe obesity results in FM having more of an influence on REE than it usually does in the non-obese population. During weight loss, the loss of large amounts of FM results in a substantial decrease of the REE [176] while REE per kg of body weight increases as the percentage of FFM increases relatively [177–180]. Although the decrease of REE seems to be explained by a change of body composition, this degree of reduction was greater than that predicted even after taking changes of body composition into account [180,181]. This further reduction was proposed as adaptive thermogenesis (AT), an adaptation mechanism allowing survival from prolonged negative energy balance by dampening overall cellular metabolic activity to preserve energy. This natural protective mechanism might have a negative impact on weight reduction and contribute to failure of further weight reduction as well as subsequent weight gain. The AT was detected after 2 weeks of energy restriction and could be observed for up to 2 years after bariatric surgery [178,182]. It was estimated that AT could result in a 120-kcal further decrease of REE from the after-weight-loss predicted REE with high individual variation) [182]. The prevalence and magnitude of AT was reported variously among different studies [183–185]. Rabl et al. even reported that no AT was detected either after bariatric surgery or with diet control [179]. These discordant results raise the hypothesis that individual factors are involved in the evolution of AT including age, sex, genetic factors, and the degree of weight loss. Discrimination between the degree of contribution on REE of skeletal muscle and those of the higher metabolically active organs (such as brain, liver, kidney) may provide more understanding in change of REE during weight loss.)

1.2.11. Geriatrics

Studies regarding energy expenditure in the geriatric population have mostly focused on the free-living elderly. The doubly-labeled water technique, together with IC, have been used commonly to explore changes of total, resting, and activity energy expenditure (AEE) during aging. Total energy expenditure (TEE) in older adults was found to decrease as compared to young adults. Its reduction was mainly contributed to by a decrease of physical activity-related energy expenditure. Many studies showed that physical activity declined with aging. One study reported a prevalence of sedentary lifestyle at 34% in older adults [186]. Chronic low physical activity can lead to loss of muscle mass which itself was found to be one of the risk factors for the decrease of activity-related energy expenditure, hence setting up a vicious cycle [187]. The AEE in elderly was reported to decrease by 2.05% each year or an average of 14.6 kcal for each day passed [187]. A large prospective 12-year cohort study in German elderly demonstrated that in each decade daily energy expenditure of physical activity decreased by 113 kcal [188].

A decrease of REE in elderly also has been reported. The loss of FFM during the aging process was proposed to be responsible for this finding. However, the decrease of REE observed in the geriatric population was not entirely explained by the effect of changes in FFM [189,190]. One study demonstrated that REE significantly declined with age even after adjustment for change of body composition and fat distribution (6.8 kcal per year in males and to 1.9 kcal per year in females, both $P < 0.001$) [188]. This finding leads to the hypothesis that there is a decrease in metabolism per unit of tissue mass accompanying the aging process. The proposed mechanism included influence of hormonal change (e.g. thyroid, catecholamine, insulin, growth hormone), qualitative change of high metabolic organ (e.g. increase in fat infiltration in the organs) [191], under-response to sympathetic activation [192], as well as a decrease in protein turn over in the elderly [189].

Despite these decreases in energy expenditure in the elderly, positive energy balance is not easily achieved particularly during hospitalization. One study revealed that the mean energy intake in hospitalized elderly patients was around 1.0 REE whereas TEE in low physical activity (i.e. lying or sitting) in the elderly was shown to be around 1.2–1.3 REE. Fifteen of twenty patients in this study showed a negative energy balance during admission which correlated with decreases of mid-arm muscle circumference [193].

Preserved energy expenditure in the elderly have been linked with their prognosis. Manini et al. demonstrated a lower mortality in free-living elderly with less decline in AEE during aging as compared to those with more decline. The highest tertile of AEE showed a significant reduction in mortality as compared to the lowest tertile (hazard ratio, 0.31; 95% confidence interval, 0.14–0.69) [87]. Higher physical activity helps to preserve muscle mass hence increase both TEE and REE in the elderly [194]. One study showed that light activity influenced on the TEE of the elderly as much as moderate to vigorous activity [195] so it should be

promoted in this population to help maintain their function and energy expenditure.

1.2.12. Diabetes mellitus

The mechanisms of increase in energy expenditure in diabetic patients are different from those found in other diseases. The disease itself does not cause intense inflammatory or catabolic state as in acute illness but alters macronutrient metabolism of the body and leads to increases in REE. Carbohydrate oxidation in diabetic patients is limited due to insulin deficiency in DM type1 or insulin resistance in DM type 2 hence the oxidation process is shifted toward lipids and proteins [63,196,197]. Lipolysis and proteolysis both are considered as a higher metabolic burden than glycolysis. Besides, increases of hepatic gluconeogenesis which is the main contributor to fasting hyperglycemia in diabetes, also consumes more energy. Many studies have demonstrated a modest increase, around 5–10%, in energy expenditure in diabetic patients in terms of REE/FFM [64,65,196,198] and by the percentage increase from the predicted value [63,67]. The degree of increase of REE showed a positive correlation with fasting plasma glucose [64] as uncontrolled disease may further aggravate lipolysis and proteolysis while this REE increment was not observed in well controlled diabetic patients [68]. Other factors that are proposed to increase energy expenditure in diabetes include increase in sympathetic activity [199]. These changes in energy expenditure may play a role in the weight loss seen in poor controlled diabetic patients in addition to dehydration and caloric loss by glycosuria.

As the pathophysiology of diabetes mellitus plays a role in increases of energy expenditure, treatments that may reverse this mechanism may be expected to have an affect in lowering energy expenditure. Insulin therapy was shown to have a negative impact on energy expenditure. After 1 year of insulin therapy which was shown to offset the increase of hepatic gluconeogenesis and lipid oxidation, patients showed an increased RQ and reduced REE [196,200]. This effect may partly be responsible for the weight gain seen after insulin therapy. Gonzalez et al. found that the reduction in REE was observed 2 days after insulin therapy was initiated. This early change in REE supported the hypothesis that the decrease in REE was caused by insulin-induced metabolic alterations rather than changes of body composition or physical activity. Furthermore, this early change in REE after treatment was associated with later weight gain during the treatment [201]. Matsushita et al. demonstrated the benefits of self-recognition of energy intake and energy expenditure in controlling blood sugar in diabetic patients [202]. Measuring REE in this group of patients may increase self-awareness of dietary control. Monitoring change in energy expenditure of diabetic patients in response to treatment may guide the selection of a hypoglycemic agent of choice which result in better weight management in obese diabetic patients.

1.2.13. Home PN patients

Patients receiving home parenteral nutrition (HPN) need particular attention regarding calorie and protein prescription as most of them present with malnutrition from various causes which resulted in the need for HPN therapy. Low body weight is common and makes them vulnerable to under- and overfeeding. Inadequate calorie intake may further deteriorate nutritional status, while overfeeding may lead to parenteral nutrition-related complications particularly liver failure. Only 1 study documenting the REE of HPN patients with IC has been performed. The mREE from 76 HPN patients was compared to common predictive equations. It was shown that 50–60% of patients would be overfed when using the predicted REE. Ireton-Jones and ESPEN 20 kcal/kg equations were the two most reliable equations to predict REE in HPN patients [90]. Additional calories should be added over the measured value to cover energy expenditure from daily activity. Edakkanambeth et al. reported energy needed for weight gain in severely underweight HPN patient was up to 50 kcal/kg/day. The amount of energy need per kg body weight decreased later during HPN therapy due to an increase of the percentage of fat mass while patients regain weight [203]. IC should be used to guide caloric prescription in this unique group of patients. Table 1 summarize the potential roles of IC as a POCT in diseases and conditions.

2. Limitations of IC measurement

Clearly, not all patients are suitable for IC measurement. De Waele et al. conducted a prospective study in critically ill patients and found 61% of patients for whom an IC measurement was indicated had conditions which precluded the measurement [93]. As IC measures inspired and expired VO_2 and expired VCO_2 for the calculation of REE, patients with any conditions which may result in O_2 and/or CO_2 losses from the circuit may be considered not good candidate for REE measurement. These conditions include those caused by diseases such as chest tube insertion with air leakage, bronchopleural fistula, and those losses due to therapeutic

Table 1
Summary of the suggested roles of IC as a point of care testing in disease and conditions.

Diseases	Possible roles of IC as a point of care testing
Acute illness	- To guide energy prescription to avoid under- and overfeeding [45,46,97,104]
Sepsis	- To determine the stage of shock and recovery [16]
	- To evaluate prognosis on mortality [114]
Multiple trauma	- To guide energy prescription to avoid overfeeding [116,117]
Postoperative	- To evaluate degree of stress caused by tissue injury after surgical procedure [60]
Traumatic brain injury	- To use mREE as a target of hypothermia therapy adjustment [120]
	- To evaluate prognosis on outcomes and to predict brain death [121]
Burn	- To use mREE as a target of metabolic-lowering interventions (pain control, sedation, adequacy of burn wound excision, temperature and humidity control, beta-adrenergic blockade) [125–129]
	- To evaluate prognosis on outcomes [133,134]
Malignancy	- To use mREE as a target of metabolic-lowering interventions [145]
	- To evaluate prognosis on outcomes and survival [83–85,135]
Cirrhosis	- To assess disease progression [71,146,148] or response to nutritional therapy [149–151]
	- To evaluate prognosis on outcomes and survival [72,204]
Renal failure	- To evaluate prognosis on outcomes and survival [169]
Obesity	- To identify patients who develop adaptive thermogenesis during weight reduction [178,182]
Geriatrics	- To evaluate prognosis on mortality [87]
Diabetes mellitus	- To early identify patients with high risk of weight gain after insulin therapy [201]
Home PN	- To guide caloric prescription during weight gaining programs [203]

interventions, i.e. high positive end expiratory pressure >10–12 cm H_2O (prone to cause leakage from the endotracheal cuff) [8,205], patients on extracorporeal membrane oxygenation (ECMO) or liver support therapy. An inaccurate measurement can occur due to limitations of the gas measurement technique [206]. The measured VO_2 is less accurate when the FiO_2 is high (considered at $FiO_2 > 60\%$) or in the presence of other gases other than O_2, CO_2, and N_2 (such as the use of NO_2 therapy). Other unstable conditions, i.e. agitation, recent analgesics and/or sedatives adjustment, change of ventilator setting, or titration of feeding within 1 h, unstable acid-base status (during renal replacement therapy), change of body temperature > 1 °C in less than 1 h, should preclude the measurement as the result may not represent a true REE. Claustrophobia can be troubling for a canopy study in non-mechanically ventilated patients.

However, certain limitations of IC have been recently been challenged. The invention of ventilator-derived REE allows REE to be calculated from only measurement of carbon dioxide provided by the built-in CO_2 sensor. Its validation compared to IC and frequently used predictive equations showed promising results in a recent study and so has been proposed as a possible solution for REE measurement where IC is not available and for the patients who require a high FiO_2 [207,208]. It should be noted that VCO_2-derived REE is based on calculated RQ which needs to be tailored to each nutrition formula, otherwise its precision may be compromised. Combining VO_2 and VCO_2 from the ventilator together with those from the artificial lung of veno-venous ECMO may allow REE to be measured in this special setting [42].

3. Conclusion

The optimization of energy provision is a mainstay of nutrition therapy. IC has been shown to be successful in determining energy expenditure, superior to all predictive equations and has become the clear gold standard in various settings. With continuous improvements in medical technology, the unwieldy face of IC has been changed to become a more compact, affordable, user-friendly, and, hence, practical option. The measurement of energy expenditure does not only provide a way to assess a patient's nutritional requirements, but also to provide clear solutions allowing the physician to adjust the caloric prescription to avoid under- and overfeeding in acute settings as well as to control the direction of long term nutritional management in chronic diseases. Studying the changes in energy expenditure over time in certain diseases has captured and revealed many subclinical metabolic alterations during disease progression or improvement. These findings may change the way we assess our patients, provide prognostic information, and may have the potential to be used as a novel metabolic treatment target. Therefore, bringing IC into clinical practice as point of care testing should be encouraged as a part of the individualized practice of modern medicine.

Acknowledgements

The authors thank Prof. J. Cohen for the English editing.

References

[1] Benedict FG, Carpenter TM. Respiration calorimeters for studying the respiratory exchange and energy transformations of man [Internet] [cited 2018 Jan 20]. Washington Carnegie Institution of Washington; 1910. p. 136. Available from:, http://archive.org/details/respirationcalor00beneuoft.
[2] Haugen HA, Chan L-N, Li F. Indirect calorimetry: a practical guide for clinicians. Nutr Clin Pract 2007 Aug 1;22(4):377–88.
[3] de Weir JBV. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949 Aug 1;109(1–2):1–9.
[4] Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009 Aug;28(4):387–400.
[5] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). J Parenter Enter Nutr 2016 Feb 1;40(2):159–211.
[6] Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. Clin Nutr 2018 Feb;37(1):336–53.
[7] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017 Feb 1;36(1):11–48.
[8] Singer P, Singer J. Clinical guide for the use of metabolic carts: indirect calorimetry—No longer the orphan of energy estimation. Nutr Clin Pract 2016 Feb 1;31(1):30–8.
[9] Siervo M, Bertoli S, Battezzati A, Wells JC, Lara J, Ferraris C, et al. Accuracy of predictive equations for the measurement of resting energy expenditure in older subjects. Clin Nutr Edinb Scotl 2014 Aug;33(4):613–9.
[10] Souza MTP, Singer P, Ozorio GA, Rosa VM, Alves MMF, Mendoza López RV, et al. Resting energy expenditure and body composition in patients with head and neck cancer: an observational study leading to a new predictive equation. Nutr Burbank Los Angel Cty Calif 2018 Aug;51–52:60–5.
[11] Zanella PB, Ávila CC, de Souza CG. Estimating resting energy expenditure by different methods as compared with indirect calorimetry for patients with pulmonary hypertension. Nutr Clin Pract Off Publ Am Soc Parenter Enter Nutr 2018 Apr;33(2):217–23.
[12] Hollander FM, Kok A, de Roos NM, Belle-van Meerkerk G, van de Graaf EA. Prediction equations underestimate resting energy expenditure in patients with end-stage cystic fibrosis. Nutr Clin Pract 2017 Feb 1;32(1):116–21.
[13] Tatucu-Babet OA, Ridley EJ, Tierney AC. Prevalence of underprescription or overprescription of energy needs in critically ill mechanically ventilated adults as determined by indirect calorimetry: a systematic literature review. J Parenter Enter Nutr 2016 Feb 1;40(2):212–25.
[14] McClave SA, DiBaise JK, Mullin GE, Martindale RG. ACG clinical guideline: nutrition therapy in the adult hospitalized patient. Am J Gastroenterol 2016 Mar;111(3):315–34. quiz 335.
[15] Long CL. Energy balance and carbohydrate metabolism in infection and sepsis. Am J Clin Nutr 1977 Aug;30(8):1301–10.
[16] Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. Crit Care Med 1993 Jul;21(7):1012–9.
[17] Vermeij CG, Feenstra BW, van Lanschot JJ, Bruining HA. Day-to-day variability of energy expenditure in critically ill surgical patients. Crit Care Med 1989 Jul;17(7):623–6.
[18] Swinamer DL, Grace MG, Hamilton SM, Jones RL, Roberts P, King EG. Predictive equation for assessing energy expenditure in mechanically ventilated critically ill patients. Crit Care Med 1990 Jun;18(6):657–61.
[19] Brandi LS, Santini L, Bertolini R, Malacarne P, Casagli S, Baraglia AM. Energy expenditure and severity of injury and illness indices in multiple trauma patients. Crit Care Med 1999 Dec;27(12):2684–9.
[20] Faisy C, Guerot E, Diehl J-L, Labrousse J, Fagon J-Y. Assessment of resting energy expenditure in mechanically ventilated patients. Am J Clin Nutr 2003 Aug;78(2):241–9.
[21] Frankenfield D, Smith JS, Cooney RN. Validation of 2 approaches to predicting resting metabolic rate in critically ill patients. JPEN J Parenter Enteral Nutr 2004 Aug;28(4):259–64.
[22] Lev S, Cohen J, Singer P. Indirect calorimetry measurements in the ventilated critically ill patient: facts and controversies—the heat is on. Crit Care Clin 2010 Oct;26(4):e1–9.
[23] Ferreira LG, Santos LF, Anastácio LR, Lima AS, Correia MITD. Resting energy expenditure, body composition, and dietary intake: a longitudinal study before and after liver transplantation. Transplantation 2013 Sep;96(6):579–85.
[24] Mitamura A, Kaneta T, Miyata G, Takanami K, Hiraide T, Fukuda H, et al. Positive correlations between tumor uptake on FDG PET and energy expenditure of patients with esophageal cancer. Ann Nucl Med 2011 May 1;25(4):241–6.
[25] Berger MM, Reintam-Blaser A, Calder PC, Casaer M, Hiesmayr MJ, Mayer K, et al. Monitoring nutrition in the ICU. Clin Nutr 2018 July 20. https://doi.org/10.1016/j.clnu.2018.07.009 [Epub ahead of print].
[26] Stucky C-CH, Moncure M, Hise M, Gossage CM, Northrop D. How accurate are resting energy expenditure prediction equations in obese trauma and burn patients? JPEN J Parenter Enteral Nutr 2008 Aug;32(4):420–6.
[27] Pantet O, Stoecklin P, Vernay A, Berger MM. Impact of decreasing energy intakes in major burn patients: a 15-year retrospective cohort study. Clin Nutr 2017;36(3):818–24.
[28] Dickerson R, Gervasio J, Riley M, Murrell J, Hickerson W, Kudsk K, et al. Accuracy of predictive methods to estimate resting energy expenditure of thermally-injured patients. J Parenter Enter Nutr 2002 Jan 1;26(1):17–29.
[29] Khorram-Sefat R, Behrendt W, Heiden A, Hettich R. Long-term measurements of energy expenditure in severe burn injury. World J Surg 1999 Feb;23(2):115–22.

[30] Royall D, Fairholm L, Peters WJ, Jeejeebhoy KN, Allard JP. Continuous measurement of energy expenditure in ventilated burn patients: an analysis. Crit Care Med 1994 Mar;22(3):399–406.
[31] Allard JP, Jeejheebhoy KN, Whitwell J, Pashutinski L, Peters WJ. Factors influencing energy expenditure in patients with burns. J Trauma 1988 Feb;28(2):199–202.
[32] Ireton CS, Turner WW, Hunt JL, Liepa GU. Evaluation of energy expenditures in burn patients. J Am Diet Assoc 1986 Mar;86(3):331–3.
[33] Allard JP, Pichard C, Hoshino E, Stechison S, Fareholm L, Peters WJ, et al. Validation of a new formula for calculating the energy requirements of burn patients. JPEN J Parenter Enteral Nutr 1990 Apr;14(2):115–8.
[34] Frankenfield DC, Ashcraft CM, Galvan DA. Longitudinal prediction of metabolic rate in critically ill patients. JPEN J Parenter Enteral Nutr 2012 Nov;36(6):700–12.
[35] McCall M, Jeejeebhoy K, Pencharz P, Moulton R. Effect of neuromuscular blockade on energy expenditure in patients with severe head injury. J Parenter Enter Nutr 2003 Jan 1;27(1):27–35.
[36] Frankenfield DC, Wiles CE, Bagley S, Siegel JH. Relationships between resting and total energy expenditure in injured and septic patients. Crit Care Med 1994 Nov;22(11):1796–804.
[37] Jeevanandam M, Young DH, Schiller WR. Obesity and the metabolic response to severe multiple trauma in man. J Clin Invest 1991 Jan;87(1):262–9.
[38] Kagan I, Cohen J, Stein M, Bendavid I, Pinsker D, Silva V, et al. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in severe multiple trauma: a prospective, randomized, double-blind study. Intensive Care Med 2015 Mar;41(3):460–9.
[39] Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. Crit Care Med 1999 Jul;27(7):1295–302.
[40] Raurich JM, Ibáñez J, Marsé P, Velasco J, Bergadá J. Energy expenditure in patients with multiple organ failure. Clin Nutr 1997 Dec 1;16(6):307–12.
[41] Raurich JM, Llompart-Pou JA, Ferreruela M, Riera M, Homar J, Marsé P, et al. A simplified equation for total energy expenditure in mechanically ventilated critically ill patients. Nutr Hosp 2015 Sep 1;32(3):1273–80.
[42] De Waele E, van Zwam K, Mattens S, Staessens K, Diltoer M, Honoré PM, et al. Measuring resting energy expenditure during extracorporeal membrane oxygenation: preliminary clinical experience with a proposed theoretical model. Acta Anaesthesiol Scand 2015 Nov;59(10):1296–302.
[43] Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study [cited 2017 Oct 21] Crit Care [Internet] 2016 Nov 10;20. Available from:, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105237/.
[44] Basile-Filho A, Auxiliadora Martins M, Marson F, Evora PRB. An easy way to estimate energy expenditure from hemodynamic data in septic patients. Acta Cir Bras 2008;23(Suppl. 1):112–7. discussion 117.
[45] Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med 2011 Apr;37(4):601–9.
[46] Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R, et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med 2017 Nov 1;43(11):1637–47.
[47] Sabatino A, Theilla M, Hellerman M, Singer P, Maggiore U, Barbagallo M, et al. Energy and protein in critically ill patients with AKI: a prospective, multicenter observational study using indirect calorimetry and protein catabolic rate [cited 2017 Sep 25] Nutrients [Internet] 2017 Aug;9(8). Available from:, https://www-ncbi-nlm-nih-gov.rproxy.tau.ac.il/pmc/articles/PMC5579596/.
[48] Hickmann CE, Roeseler J, Castanares-Zapatero D, Herrera EI, Mongodin A, Laterre P-F. Energy expenditure in the critically ill performing early physical therapy. Intensive Care Med 2014 Apr 1;40(4):548–55.
[49] Swinamer DL, Phang PT, Jones RL, Grace M, King EG. Twenty-four hour energy expenditure in critically ill patients. Crit Care Med 1987 Jul;15(7):637–43.
[50] Frankenfield DC, Oniert LA, Badellino MM, Wiles CE, Bagley SM, Goodarzi S, et al. Correlation between measured energy expenditure and clinically obtained variables in trauma and sepsis patients. J Parenter Enter Nutr 1994 Sep 1;18(5):398–403.
[51] Panitchote A, Thiangpak N, Hongsprabhas P, Hurst C. Energy expenditure in severe sepsis or septic shock in a Thai medical intensive care unit. Asia Pac J Clin Nutr 2017;26(5):794–7.
[52] Subramaniam A, McPhee M, Nagappan R. Predicting energy expenditure in sepsis: Harris-Benedict and Schofield equations versus the Weir derivation. Crit Care Resusc J Australas Acad Crit Care Med 2012 Sep;14(3):202–10.
[53] Rusavy Z, Sramek V, Lacigova S, Novak I, Tesinsky P, Macdonald IA. Influence of insulin on glucose metabolism and energy expenditure in septic patients. Crit Care 2004 Aug;8(4):R213–20.
[54] Osuka A, Uno T, Nakanishi J, Hinokiyama H, Takahashi Y, Matsuoka T. Energy expenditure in patients with severe head injury: controlled normothermia with sedation and neuromuscular blockade. J Crit Care 2013 Apr 1;28(2).218.e9-218.e13.
[55] Bruder N, Lassegue D, Pelissier D, Graziani N, François G. Energy expenditure and withdrawal of sedation in severe head-injured patients. Crit Care Med 1994 Jul;22(7):1114–9.
[56] Bruder N, Raynal M, Pellissier D, Courtinat C, François G. Influence of body temperature, with or without sedation, on energy expenditure in severe head-injured patients. Crit Care Med 1998 Mar;26(3):568–72.
[57] McEvoy CT, Cran GW, Cooke SR, Young IS. Resting energy expenditure in non-ventilated, non-sedated patients recovering from serious traumatic brain injury: comparison of prediction equations with indirect calorimetry values. Clin Nutr 2009 Oct 1;28(5):526–32.
[58] Brandi LS, Oleggini M, Lachi S, Frediani M, Bevilacqua S, Mosca F, et al. Energy metabolism of surgical patients in the early postoperative period: a reappraisal. Crit Care Med 1988 Jan;16(1):18–22.
[59] Fredrix EWHM, Soeters PB, Von Meyenfeldt MF, Saris WHM. Resting energy expenditure in cancer patients before and after gastrointestinal surgery. J Parenter Enter Nutr 1991 Nov 1;15(6):604–7.
[60] Yatabe T, Kitagawa H, Yamashita K, Hanazaki K, Yokoyama M. Energy expenditure measured using indirect calorimeter after minimally invasive esophagectomy in ventilated postoperative patients. Asia Pac J Clin Nutr 2014;23(4):555–9.
[61] Martins MA, Menegueti MG, Nicolini EA, Picolo MF, Lago AF, Filho M, et al. Energy expenditure in critically ill surgical patients. Comparative analysis of predictive equation and indirect calorimetry. Acta Cir Bras 2011;26:51–6.
[62] Suen J, Thomas JM, Delaney CL, Spark JI, Miller MD. Estimating energy expenditure in vascular surgery patients: are predictive equations accurate enough? Clin Nutr ESPEN 2016 Dec;16:16–23.
[63] Nair KS, Halliday D, Garrow JS. Increased energy expenditure in poorly controlled Type 1 (insulin-dependent) diabetic patients. Diabetologia 1984 Jul;27(1):13–6.
[64] Buscemi S, Donatelli M, Grosso G, Vasto S, Galvano F, Costa F, et al. Resting energy expenditure in type 2 diabetic patients and the effect of insulin bolus. Diabetes Res Clin Pract 2014 Dec;106(3):605–10.
[65] Bitz C, Toubro S, Larsen TM, Harder H, Rennie KL, Jebb SA, et al. Increased 24-h energy expenditure in type 2 diabetes. Diabetes Care 2004 Oct 1;27(10):2416–21.
[66] Ikeda K, Fujimoto S, Goto M, Yamada C, Hamasaki A, Ida M, et al. A new equation to estimate basal energy expenditure of patients with diabetes. Clin Nutr 2013 Oct;32(5):777–82.
[67] Fontvieille AM, Lillioja S, Ferraro RT, Schulz LO, Rising R, Ravussin E. Twenty-four-hour energy expenditure in pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1992 Aug 1;35(8):753–9.
[68] Ryan M, Sallé A, Guilloteau G, Genaitay M, Livingstone MBE, Ritz P. Resting energy expenditure is not increased in mildly hyperglycaemic obese diabetic patients. Br J Nutr 2006 Nov;96(5):945–8.
[69] Teramoto A, Yamanaka-Okumura H, Urano E, Nakamura-Kutsuzawa T, Sugihara K, Katayama T, et al. Comparison of measured and predicted energy expenditure in patients with liver cirrhosis. Asia Pac J Clin Nutr 2014;23(2):197–204.
[70] Tajika M, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition 2002 Mar 1;18(3):229–34.
[71] Mathur S, Peng S, Gane EJ, McCall JL, Plank LD. Hypermetabolism predicts reduced transplant-free survival independent of MELD and child-pugh scores in liver cirrhosis. Nutrition 2007 May;23(5):398–403.
[72] Selberg O, Bottcher J, Tusch G, Pichlmayr R, Henkel E, Muller MJ. Identification of high- and low-risk patients before liver transplantation: a prospective cohort study of nutritional and metabolic parameters in 150 patients. Hepatology 1997 Mar 1;25(3):652–7.
[73] Belarmino G, Singer P, Gonzalez MC, Machado NM, Cardinelli CS, Barcelos S, et al. Prognostic value of energy expenditure and respiratory quotient measuring in patients with liver cirrhosis. Clin Nutr [Internet] 2018 Jul 6 [cited 2018 Jul 10]; Available from: http://www.sciencedirect.com/science/article/pii/S0261561418312020.
[74] Dolz C, Raurich JM, Ibanez J, Obrador A, Marse P, Gaya J. Ascites increases the resting energy expenditure in liver cirrhosis. Gastroenterology 1991 Jan 1;100(3):738–44.
[75] Müller MJ, Böker KHW, Selberg O. Are patients with liver cirrhosis hypermetabolic? Clin Nutr 1994 Jun 1;13(3):131–44.
[76] Kamimura MA, Avesani CM, Bazanelli AP, Baria F, Draibe SA, Cuppari L. Are prediction equations reliable for estimating resting energy expenditure in chronic kidney disease patients? Nephrol Dial Transplant 2011 Feb 1;26(2):544–50.
[77] Vilar E, Machado A, Garrett A, Kozarski R, Wellsted D, Farrington K. Disease-specific predictive formulas for energy expenditure in the dialysis population. J Ren Nutr 2014 Jul 1;24(4):243–51.
[78] Lee SW, Kim HJ, Kwon HK, Son SM, Song JH, Kim M-J. Agreements between indirect calorimetry and prediction equations of resting energy expenditure in end-stage renal disease patients on continuous ambulatory peritoneal dialysis. Yonsei Med J 2008 Apr 30;49(2):255.
[79] Byham-Gray L, Parrott JS, Ho WY, Sundell MB, Ikizler TA. Development of a predictive energy equation for maintenance hemodialysis patients: a pilot study [cited 2017 Sep 27] J Ren Nutr Off J Counc Ren Nutr Natl Kidney Found [Internet] 2014 Jan;24(1). Available from:, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883673/.
[80] Cuppari L, de Carvalho AB, Avesani CM, Kamimura MA, dos S Lobão RR, Draibe SA. Increased resting energy expenditure in hemodialysis patients with severe hyperparathyroidism. J Am Soc Nephrol 2004 Nov 1;15(11):2933–9.

[81] Fredrix EW, Soeters PB, Wouters EF, Deerenberg IM, von Meyenfeldt MF, Saris WH. Effect of different tumor types on resting energy expenditure. Cancer Res 1991 Nov 15;51(22):6138–41.

[82] Pirat A, Tucker AM, Taylor KA, Jinnah R, Finch CG, Canada TD, et al. Comparison of measured versus predicted energy requirements in critically ill cancer patients. Respir Care 2009 Apr 1;54(4):487–94.

[83] Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, et al. Resting energy expenditure in the risk assessment of anticancer treatments. Clin Nutr [Internet] 2017 Jan 19 [cited 2017 Oct 11]; Available from: http://www.sciencedirect.com/science/article/pii/S0261561417300122.

[84] Vazeille C, Jouinot A, Durand J-P, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr 2017 May 1;105(5):1139–47.

[85] Jatoi A, Daly BDT, Hughes V, Dallal GE, Roubenoff R. The prognostic effect of increased resting energy expenditure prior to treatment for lung cancer. Lung Cancer 1999 Feb 1;23(2):153–8.

[86] Sergi G, Coin A, Mulone S, Castegnaro E, Giantin V, Manzato E, et al. Resting energy expenditure and body composition in bedridden institutionalized elderly women with advanced-stage pressure sores. J Gerontol Ser A 2007 Mar 1;62(3):317–22.

[87] Manini TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, et al. Daily activity energy expenditure and mortality among older adults. JAMA 2006 Jul 12;296(2):171–9.

[88] Anbar R, Beloosesky Y, Cohen J, Madar Z, Weiss A, Theilla M, et al. Tight calorie control in geriatric patients following hip fracture decreases complications: a randomized, controlled study. Clin Nutr 2014 Feb;33(1):23–8.

[89] Alfonzo-González G, Doucet E, Bouchard C, Tremblay A. Greater than predicted decrease in resting energy expenditure with age: cross-sectional and longitudinal evidence. Eur J Clin Nutr 2006 Jan;60(1):18–24.

[90] Ławiński M, Singer P, Gradowski Ł, Gradowska A, Bzikowska A, Majewska K. Predicted versus measured resting energy expenditure in patients requiring home parenteral nutrition. Nutrition 2015 Dec;31(11–12):1328–32.

[91] Hipskind P, Glass C, Charlton D, Nowak D, Dasarathy S. Do handheld calorimeters have a role in assessment of nutrition needs in hospitalized patients? A systematic review of literature. Nutr Clin Pract Off Publ Am Soc Parenter Enter Nutr 2011 Aug;26(4):426–33.

[92] Frankenfield DC, Coleman A. An evaluation of a handheld indirect calorimeter against a standard calorimeter in obese and nonobese adults. J Parenter Enter Nutr 2013 Sep 1;37(5):652–8.

[93] De Waele E, Spapen H, Honoré PM, Mattens S, Van Gorp V, Diltoer M, et al. Introducing a new generation indirect calorimeter for estimating energy requirements in adult intensive care unit patients: feasibility, practical considerations, and comparison with a mathematical equation. J Crit Care 2013 Oct;28(5):884.e1–6.

[94] Japur CC, Monteiro JP, Marchini JS, Garcia RWD, Basile-Filho A. Can an adequate energy intake be able to reverse the negative nitrogen balance in mechanically ventilated critically ill patients? J Crit Care 2010 Sep 1;25(3):445–50.

[95] Berg A, Rooyackers O, Bellander B-M, Wernerman J. Whole body protein kinetics during hypocaloric and normocaloric feeding in critically ill patients. Crit Care 2013 Jul 24;17(4):R158.

[96] Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. Clin Nutr 2006 Feb;25(1):37–44.

[97] Petros Sirak, Horbach Monika, Seidel Frank, Weidhase Lorenz. Hypocaloric vs Normocaloric nutrition in critically ill patients: a prospective randomized pilot trial. J Parenter Enter Nutr 2016 Feb 1;40(2):242–9.

[98] Faisy C, Lerolle N, Dachraoui F, Savard J-F, Abboud I, Tadie J-M, et al. Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. Br J Nutr 2009 Apr;101(7):1079–87.

[99] Villet S, Chiolero RL, Bollmann MD, Revelly J-P, Cayeux RNM-C, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr Edinb Scotl 2005 Aug;24(4):502–9.

[100] Weijs PJM, Stapel SN, de Groot SDW, Driessen RH, de Jong E, Girbes ARJ, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr 2012 Jan;36(1):60–8.

[101] McClave SA, McClain CJ, Snider HL. Should indirect calorimetry be used as part of nutritional assessment? J Clin Gastroenterol 2001 Jul;33(1):14–9.

[102] Dissanaike S, Shelton M, Warner K, O'Keefe GE. The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. Crit Care Lond Engl 2007;11(5):R114.

[103] Grau-Carmona T, Morán-García V, García-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, López-Martínez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. Clin Nutr Edinb Scotl 2011 Oct;30(5):578–84.

[104] Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013 Feb 2;381(9864):385–93.

[105] Maxwell J, Gwardschaladse C, Lombardo G, Petrone P, Policastro A, Karev D, et al. The impact of measurement of respiratory quotient by indirect calorimetry on the achievement of nitrogen balance in patients with severe traumatic brain injury. Eur J Trauma Emerg Surg 2016 Sep 22:1–8.

[106] Cuthbertson DP. Post-shock metabolic response. Lancet 1942 Apr 11;239(6189):433–7.

[107] Plank LD, Hill GL. Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. World J Surg 2000 Jun;24(6):630–8.

[108] Plank LD, Connolly AB, Hill GL. Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. Ann Surg 1998 Aug;228(2):146.

[109] Botrán M, López-Herce J, Mencía S, Urbano J, Solana MJ, García A, et al. Relationship between energy expenditure, nutritional status and clinical severity before starting enteral nutrition in critically ill children. Br J Nutr 2011 Mar;105(5):731–7.

[110] De Backer D, Creteur J, Preiser J-C, Dubois M-J, Vincent J-L. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 2002 Jul 1;166(1):98–104.

[111] Edul VSK, Enrico C, Laviolle B, Vazquez AR, Ince C, Dubin A. Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. Crit Care Med 2012 May;40(5):1443–8.

[112] Feferbaum R, Leone C, Siqueira AA, Valenti VE, Gallo PR, Reis AO, et al. Rest energy expenditure is decreased during the acute as compared to the recovery phase of sepsis in newborns. Nutr Metabol 2010;7:63.

[113] Briassoulis G, Venkataraman S, Thompson AE. Energy expenditure in critically ill children. Crit Care Med 2000 Apr;28(4):1166–72.

[114] Wu C, Wang X, Yu W, Tian F, Liu S, Li P, et al. Hypermetabolism in the initial phase of intensive care is related to a poor outcome in severe sepsis patients. Ann Nutr Metabol 2015;66(4):188–95.

[115] Baker SP, O'Neill B. The injury severity score: an update. J Trauma 1976 Nov;16(11):882–5.

[116] Frankenfield DC, Smith JS, Cooney RN. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. J Parenter Enter Nutr 1997 Nov 1;21(6):324–9.

[117] Huschak G, Zur Nieden K, Hoell T, Riemann D, Mast H, Stuttmann R. Olive oil based nutrition in multiple trauma patients: a pilot study. Intensive Care Med 2005 Sep;31(9):1202–8.

[118] Foley N, Marshall S, Pikul J, Salter K, Teasell R. Hypermetabolism following moderate to severe traumatic acute brain injury: a systematic review. J Neurotrauma 2008 Dec;25(12):1415–31.

[119] Sunderland PM, Heilbrun MP. Estimating energy expenditure in traumatic brain injury: comparison of indirect calorimetry with predictive formulas. Neurosurgery 1992 Aug;31(2):246–52. discussion 252-253.

[120] Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. Neurosurgery 2003 Jan;52(1):102–11. discussion 111-112.

[121] Bitzani M, Matamis D, Nalbandi V, Vakalos A, Karasakalides A, Riggos D. Resting energy expenditure in brain death. Intensive Care Med 1999 Sep;25(9):970–6.

[122] Xie WG, Li A, Wang SL. Estimation of the calorie requirements of burned Chinese adults. Burns J Int Soc Burn Inj 1993 Apr;19(2):146–9.

[123] Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. J Parenter Enter Nutr 1979 Nov 1;3(6):452–6.

[124] Harrison TS, Seaton JF, Feller I. Relationship of increased oxygen consumption to catecholamine excretion in thermal burns. Ann Surg 1967 Feb;165(2):169–72.

[125] Wilmore DW, Long JM, Mason AD, Skreen RW, Pruitt BA. Catecholamines: mediator of the hypermetabolic response to thermal injury. Ann Surg 1974 Oct;180(4):653–68.

[126] Demling RH, Lalonde C. Effect of partial burn excision and closure on post-burn oxygen consumption. Surgery 1988 Nov;104(5):846–52.

[127] Chai J, Sheng Z, Gao J. The effects of extensive excision of massive invasive infected burn wound on the REE of burn patients with sepsis. Zhonghua Shao Shang Za Zhi Zhonghua Shaoshang Zazhi Chin J Burns 2001 Apr;17(2):96–8.

[128] Wilmore DW, Mason AD, Johnson DW, Pruitt BA. Effect of ambient temperature on heat production and heat loss in burn patients. J Appl Physiol 1975 Apr;38(4):593–7.

[129] Caldwell Jr FT. Control of the hypermetabolic response to burn injury using environmental factors. Ann Surg 1992 May;215(5):485.

[130] Xi P, Kaifa W, Yong Z, Hong Y, Chao W, Lijuan S, et al. Establishment and assessment of new formulas for energy consumption estimation in adult burn patients. PLoS One 2014;9(10):e110409.

[131] Milner EA, Cioffi WG, Mason AD, McManus WF, Pruitt BA. A longitudinal study of resting energy expenditure in thermally injured patients. J Trauma 1994 Aug;37(2):167–70.

[132] Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, et al. Persistence of muscle catabolism after severe burn. Surgery 2000 Aug 1;128(2):312–9.

[133] Hart DW, Wolf SE, Herndon DN, Chinkes DL, Lal SO, Obeng MK, et al. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. Ann Surg 2002 Jan;235(1):152.

[134] Jeschke MG, Gauglitz GG, Finnerty CC, Kraft R, Mlcak RP, Herndon DN. Survivors versus non-survivors postburn: differences in inflammatory and hypermetabolic trajectories. Ann Surg 2014 Apr;259(4):814–23.

[135] Bosaeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. J Nutr 2002 Nov 1;132(11):3465S–6S.

[136] Chen W-J, Chung Y-C. Energy expenditure in patients with hepatocellular carcinoma. Cancer 1994 Feb 1;73(3):590–5.

[137] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011 Mar 4;144(5):646–74.

[138] Zu XL, Guppy M. Cancer metabolism: facts, fantasy, and fiction. Biochem Biophys Res Commun 2004 Jan 16;313(3):459–65.

[139] Warburg O. On the origin of cancer cells. Science 1956 Feb 24;123(3191):309–14.

[140] Holroyde CP, Gabuzda TG, Putnam RC, Paul P, Reichard GA. Altered glucose metabolism in metastatic carcinoma. Cancer Res 1975 Dec;35(12):3710–4.

[141] Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia [cited 2017 Oct 11] Theor Biol Med Model [Internet] 2015;12. Available from:, https://www-ncbi-nlm-nih-gov.rproxy.tau.ac.il/pmc/articles/PMC4570294/.

[142] Wu J, Huang C, Xiao H, Tang Q, Cai W. Weight loss and resting energy expenditure in male patients with newly diagnosed esophageal cancer. Nutrition 2013 Dec;29(11–12):1310–4.

[143] Cao D, Wu G, Zhang B, Quan Y, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr 2010 Feb;29(1):72–7.

[144] Dominguez N, Canada T. Considerations in hypermetabolism, cachexia, and survival in cancer. Am J Clin Nutr 2017 Sep 1;106(3):957–8.

[145] Ma Y-J, Yu J, Xiao J, Cao B-W. The consumption of omega-3 polyunsaturated fatty acids improves clinical outcomes and prognosis in pancreatic cancer patients: a systematic evaluation. Nutr Cancer 2015;67(1):112–8.

[146] Korenaga K, Korenaga M, Teramoto F, Suzuki T, Nishina S, Sasaki K, et al. Clinical usefulness of non-protein respiratory quotient measurement in non-alcoholic fatty liver disease. Hepatol Res Off J Jpn Soc Hepatol 2013 Dec;43(12):1284–94.

[147] Nishikawa H, Yoh K, Enomoto H, Iwata Y, Kishino K, Shimono Y, et al. Factors associated with protein-energy malnutrition in chronic liver disease: analysis using indirect calorimetry [cited 2017 Oct 15] Medicine (Baltimore) [Internet] 2016 Jan;95(2). Available from:, https://www-ncbi-nlm-nih-gov.rproxy.tau.ac.il/pmc/articles/PMC4718256/.

[148] Nishikawa H, Enomoto H, Iwata Y, Kishino K, Shimono Y, Hasegawa K, et al. Prognostic significance of nonprotein respiratory quotient in patients with liver cirrhosis [cited 2017 Oct 11] Medicine (Baltimore) [Internet] 2017 Jan;96(3). Available from:, https://www-ncbi-nlm-nih-gov.rproxy.tau.ac.il/pmc/articles/PMC5279081/.

[149] Harima Y, Yamasaki T, Hamabe S, Saeki I, Okita K, Terai S, et al. Effect of a late evening snack using branched-chain amino acid-enriched nutrients in patients undergoing hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma. Hepatol Res 2010 Jun;40(6):574–84.

[150] Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition 2007 Feb 1;23(2):113–20.

[151] Yamanaka-Okumura H, Nakamura T, Takeuchi H, Miyake H, Katayama T, Arai H, et al. Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. Eur J Clin Nutr 2006 Sep;60(9):1067–72.

[152] Sugihara K, Yamanaka-Okumura H, Teramoto A, Urano E, Katayama T, Morine Y, et al. Recovery of nutritional metabolism after liver transplantation. Nutrition 2015 Jan 1;31(1):105–10.

[153] McCullough AJ, Raguso C. Effect of cirrhosis on energy expenditure. Am J Clin Nutr 1999 Jun 1;69(6):1066–8.

[154] Merli M, Riggio O, Romiti A, Ariosto F, Mango L, Pinto G, et al. Basal energy production rate and substrate use in stable cirrhotic patients. Hepatology 1990 Jul 1;12(1):106–12.

[155] Müller MJ, Böttcher J, Selberg O, Weselmann S, Böker KH, Schwarze M, et al. Hypermetabolism in clinically stable patients with liver cirrhosis. Am J Clin Nutr 1999 Jun 1;69(6):1194–201.

[156] Lee WG, McCall JL, Gane EJ, Murphy R, Plank LD. Oral β-blockade in relation to energy expenditure in clinically stable patients with liver cirrhosis: a double-blind randomized cross-over trial. Metabolism 2012 Nov 1;61(11):1547–53.

[157] Avesani CM, Draibe SA, Kamimura MA, Dalboni MA, Colugnati FAB, Cuppari L. Decreased resting energy expenditure in non-dialysed chronic kidney disease patients. Nephrol Dial Transplant 2004 Dec 1;19(12):3091–7.

[158] O'Sullivan AJ, Lawson JA, Chan M, Kelly JJ. Body composition and energy metabolism in chronic renal insufficiency. Am J Kidney Dis Off J Natl Kidney Found 2002 Feb;39(2):369–75.

[159] Cuppari L, Ikizler TA. Energy balance in advanced chronic kidney disease and end-stage renal disease. Semin Dial 2010 Aug 7;23(4):373–7.

[160] Schneeweiss B, Graninger W, Stockenhuber F, Druml W, Ferenci P, Eichinger S, et al. Energy metabolism in acute and chronic renal failure. Am J Clin Nutr 1990 Oct;52(4):596–601.

[161] Panesar A, Agarwal R. Resting energy expenditure in chronic kidney disease: relationship with glomerular filtration rate. Clin Nephrol 2003 May;59(5):360–6.

[162] Neyra R, Chen K, Sun M, Shyr Y, Hakim R, Ikizler T. Increased resting energy expenditure in patients with end-stage renal disease. J Parenter Enter Nutr 2003 Jan 1;27(1):36–42.

[163] Sridharan S, Vilar E, Berdeprado J, Farrington K. Energy metabolism, body composition, and urea generation rate in hemodialysis patients. Hemodial Int 2013 Oct 1;17(4):502–9.

[164] Avesani CM, Draibe SA, Kamimura MA, Colugnati FAB, Cuppari L. Resting energy expenditure of chronic kidney disease patients: influence of renal function and subclinical inflammation. Am J Kidney Dis Off J Natl Kidney Found 2004 Dec;44(6):1008–16.

[165] Ikizler TA, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RM. Increased energy expenditure in hemodialysis patients. J Am Soc Nephrol 1996 Dec 1;7(12):2646–53.

[166] Kamimura MA, Draibe SA, Avesani CM, Canziani MEF, Colugnati F a B, Cuppari L. Resting energy expenditure and its determinants in hemodialysis patients. Eur J Clin Nutr 2007 Mar;61(3):362.

[167] Mafra D, Deleaval P, Teta D, Cleaud C, Arkouche W, Jolivot A, et al. Influence of inflammation on total energy expenditure in hemodialysis patients. J Ren Nutr Off J Counc Ren Nutr Natl Kidney Found 2011 Sep;21(5):387–93.

[168] Kogirima M, Sakaguchi K, Nishino K, Ichikawa Y, Hiramatsu F, Yamamoto S. Low resting energy expenditure in middle-aged and elderly hemodialysis patients with poor nutritional status. J Med Investig JMI 2006 Feb;53(1–2):34–41.

[169] Wang AY-M, Sea MM-M, Tang N, Sanderson JE, Lui S-F, Li PK-T, et al. Resting energy expenditure and subsequent mortality risk in peritoneal dialysis patients. J Am Soc Nephrol 2004 Dec 1;15(12):3134–43.

[170] Wang AY-M, Sea MM-M, Tang N, Lam CW, Chan IH-S, Lui S-F, et al. Energy intake and expenditure profile in chronic peritoneal dialysis patients complicated with circulatory congestion. Am J Clin Nutr 2009 Nov 1;90(5):1179–84.

[171] Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. Am J Clin Nutr 2005 Oct 1;82(4):801–5.

[172] de Góes CR, Sanches ACS, Balbi A, Ponce D, de Góes CR, Sanches ACS, et al. Daily variability of resting energy expenditure in acute kidney injury patients on dialysis. J Bras Nefrol 2017 Mar;39(1):15–22.

[173] de Góes CR, Vogt BP, Sanches ACS, Balbi AL, Ponce D. Influence of different dialysis modalities in the measurement of resting energy expenditure in patients with acute kidney injury in ICU. Clin Nutr 2017 Aug;36(4):1170–4.

[174] de Góes CR, Berbel-Bufarah MN, Sanches ACS, Xavier PS, Balbi AL, Ponce D. Poor agreement between predictive equations of energy expenditure and measured energy expenditure in critically ill acute kidney injury patients. Ann Nutr Metabol 2016;68(4):276–84.

[175] Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, et al. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring continuous renal replacement therapy. Nutrition 2003;19(11–12):909–16.

[176] Browning MG, Franco RL, Cyrus JC, Celi F, Evans RK. Changes in resting energy expenditure in relation to body weight and composition following gastric restriction: a systematic review. Obes Surg 2016 Jul;26(7):1607–15.

[177] Werling M, Fändriks L, Olbers T, Bueter M, Sjöström L, Lönroth H, et al. Roux-en-Y gastric bypass surgery increases respiratory quotient and energy expenditure during food intake. PLoS One 2015;10(6):e0129784.

[178] Tam CS, Rigas G, Heilbronn LK, Matisan T, Probst Y, Talbot M. Energy adaptations persist 2 years after sleeve gastrectomy and gastric bypass. Obes Surg 2016 Feb;26(2):459–63.

[179] Rabl C, Rao MN, Schwarz J-M, Mulligan K, Campos GM. Thermogenic changes after gastric bypass, adjustable gastric banding or diet alone. Surgery 2014 Oct;156(4):806–12.

[180] Johannsen DL, Knuth ND, Huizenga R, Rood JC, Ravussin E, Hall KD. Metabolic slowing with massive weight loss despite preservation of fat-free mass. J Clin Endocrinol Metabol 2012 Jul 1;97(7):2489–96.

[181] Coupaye M, Bouillot J-L, Coussieu C, Guy-Grand B, Basdevant A, Oppert J-M. One-year changes in energy expenditure and serum leptin following adjustable gastric banding in obese women. Obes Surg 2005 Jul;15(6):827–33.

[182] Müller M j, Bosy-Westphal A. Adaptive thermogenesis with weight loss in humans. Obesity 2013 Feb 1;21(2):218–28.

[183] Goele K, Bosy-Westphal A, Rumcker B, Lagerpusch M, Muller MJ. Influence of changes in body composition and adaptive thermogenesis on the difference between measured and predicted weight loss in obese women. Obes Facts 2009;2(2):105–9.

[184] Bosy-Westphal A, Kossel E, Goele K, Later W, Hitze B, Settler U, et al. Contribution of individual organ mass loss to weight loss-associated decline in resting energy expenditure. Am J Clin Nutr 2009 Oct;90(4):993–1001.

[185] Lagerpusch M, Bosy-Westphal A, Kehden B, Peters A, Müller MJ. Effects of brief perturbations in energy balance on indices of glucose homeostasis in healthy lean men. Int J Obes 2005 2012 Aug;36(8):1094–101.

[186] Ramalho JR de O, Lima-Costa MF, Firmo JOA, Peixoto SV. Energy expenditure through physical activity in a population of community-dwelling Brazilian elderly: cross-sectional evidences from the Bambuí cohort study of aging. Cad Saúde Pública 2011;27(Suppl. 3):S399–408.

[187] Valiani V, Sourdet S, Schoeller DA, Mackey DC, Bauer DC, Glynn NW, et al. Surveying predictors of late-life longitudinal change in daily activity energy expenditure. PLoS One 2017 Oct 17;12(10):e0186289.
[188] Lührmann PM, Bender R, Edelmann-Schäfer B, Neuhäuser-Berthold M. Longitudinal changes in energy expenditure in an elderly German population: a 12-year follow-up. Eur J Clin Nutr 2009 Aug;63(8):986.
[189] Pannemans DL, Westerterp KR. Energy expenditure, physical activity and basal metabolic rate of elderly subjects. Br J Nutr 1995 Apr;73(4):571–81.
[190] Rothenberg EM, Bosaeus IG, Westerterp KR, Steen BC. Resting energy expenditure, activity energy expenditure and total energy expenditure at age 91–96 years. Br J Nutr 2000 Sep;84(3):319–24.
[191] Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, et al. Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. Am J Physiol 1998 Aug;275(2 Pt 1):E249–58.
[192] Heinsimer JA, Lefkowitz RJ. The impact of aging on adrenergic receptor function: clinical and biochemical aspects. J Am Geriatr Soc 1985 Mar;33(3):184–8.
[193] Klipstein-Grobusch K, Reilly JJ, Potter J, Edwards CA, Roberts MA. Energy intake and expenditure in elderly patients admitted to hospital with acute illness. Br J Nutr 1995 Feb;73(2):323–34.
[194] Hunter GR, Wetzstein CJ, Fields DA, Brown A, Bamman MM. Resistance training increases total energy expenditure and free-living physical activity in older adults. J Appl Physiol Bethesda Md 1985 2000 Sep;89(3):977–84.
[195] Colbert LH, Matthews CE, Schoeller DA, Havighurst TC, Kim K. Intensity of physical activity in the energy expenditure of older adults. J Aging Phys Activ 2014 Oct;22(4):571–7.
[196] Franssila-Kallunki A, Groop L. Factors associated with basal metabolic rate in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1992 Oct;35(10):962–6.
[197] Gougeon R, Morais JA, Chevalier S, Pereira S, Lamarche M, Marliss EB. Determinants of whole-body protein metabolism in subjects with and without type 2 diabetes. Diabetes Care 2008 Jan;31(1):128–33.
[198] Ikeda K, Fujimoto S, Goto M, Yamada C, Hamasaki A, Shide K, et al. Impact of endogenous and exogenous insulin on basal energy expenditure in patients with type 2 diabetes under standard treatment. Am J Clin Nutr 2011 Dec 1;94(6):1513–8.
[199] Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF, Mary DASG. Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. Circulation 2003 Dec 23;108(25):3097–101.
[200] Mäkimattila S, Nikkilä K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus. Diabetologia 1999 Apr;42(4):406–12.
[201] Gonzalez C, Fagour C, Maury E, Cherifi B, Salandini S, Pierreisnard A, et al. Early changes in respiratory quotient and resting energy expenditure predict later weight changes in patients treated for poorly controlled type 2 diabetes. Diabetes Metabol 2014 Sep;40(4):299–304.
[202] Matsushita Y, Yokoyama T, Homma T, Tanaka H, Kawahara K. Relationship between the ability to recognize energy intake and expenditure, and blood sugar control in type 2 diabetes mellitus patients. Diabetes Res Clin Pract 2005 Mar;67(3):220–6.
[203] Edakkanambeth Varayil J, Hurt RT, Kelly DG. How hyperalimentation may be necessary to reverse severe malnutrition in selected patients receiving home parenteral nutrition. Nutr Clin Pract 2014 Apr 1;29(2):229–33.
[204] Blarmino G, Singer P, Gonzalez MC, Torrinhas RSM, Andraus W, D'Albuquerque L, et al. Predictive value of measured energy expenditure in cirrhosis patients. Clin Nutr 2018 July 6. https://doi.org/10.1016/j.clnu/2018.07.001 [Epub ahead of print].
[205] Oshima T, Berger MM, Waele ED, Guttormsen AB, Heidegger C-P, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr 2017 Jun 1;36(3):651–62.
[206] Takala J, Keinänen O, Väisänen P, Kari A. Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. Crit Care Med 1989 Oct;17(10):1041–7.
[207] Stapel SN, de Grooth H-JS, Alimohamad H, Elbers PWG, Girbes ARJ, Weijs PJM, et al. Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: proof of concept. Crit Care 2015 Oct 22;19:370.
[208] Mehta NM, Smallwood CD, Joosten KFM, Hulst JM, Tasker RC, Duggan CP. Accuracy of a simplified equation for energy expenditure based on bedside volumetric carbon dioxide elimination measurement – a two-center study. Clin Nutr 2015 Feb;34(1):151.