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EDITORIAL

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Energy deficit is clinically relevant for critically ill patients: yes

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Energy is essential for life

Survival mechanisms have evolved for thousand of years to optimize vital energy-dependent functions at the expense of substrates stored in lean and fat tissues. A phylogenic analysis of mammalian biology supports the concept that human beings challenged by life-threatening conditions have been programed for energy autonomy for a few days only, as the absence of hydration for 4–5 days defines the survival limit. Beyond this limit, both water and some energy are needed for further survival and functional recovery. In addition, only the strongest and youngest individuals were likely to survive, as the ultimate goal was the reproduction of the species. Energy deficit promotes proteolysis and lipolysis to fuel the mandatory gluconeogenesis, which rapidly deteriorates most of the vital body functions (e.g., muscle strength, physical mobility, thermic control, immune response, etc.). This deficit induces auto-cannibalism, a short-term, life-saving, genetically driven mechanism, but also a condition compromising recovery and increasing morbidity and ultimately mortality [1, 2].

In 2015, the mean age of ICU patients and the number of those with one or more chronic diseases and/or sarcopenic obesity have significantly increased. Life support techniques have increased survival up to a point where the nutritional condition becomes a limiting factor for the clinical outcome. A "simple" nutritional support adapted to the body's needs and enabling a positive response to the sophisticated treatments would be highly desirable.

Unrecognized overfeeding has created confusion

The above considerations largely explain why the early prescription of enteral nutrition (EN) has been repeatedly associated with improved clinical outcome largely owing to non-nutritional and nutritional benefits [3]. Indeed the limited and progressive tolerance to EN observed during the first days after trauma or critical illness favors progressive energy provision, which fits the natural evolution of the metabolic stress. Enteral nutrition intolerance is frequently observed (i.e., vomiting, diarrhea) [4]. Contrariwise, parenteral nutrition (PN) administered during the early phase of stress often results in unrecognized adverse effects associated with overfeeding, because metabolic alterations require careful biological monitoring which is frequently overlooked [5]. Discrepancies exist in the literature about the impact of EN and PN on clinical outcome. Most of them result from inadequate definition of the energy target, delayed use of EN, or inappropriate use of PN [6].

Table 1 Comparison of the latest published nutrition trials: energy target determination and limitations

	Casaer et al. [7] EPaNIC	Doig et al. [9] Early PN	Harvey et al. [10] Nutrition route	Heidegger et al. [12] Swiss SPN	Singer et al. [15] TICACOS	Petros et al. [16] Hypocal vs isocal	Arabi et al. [18] Permissive underfeeding
n	4,660	1,361	2,383	305	130	100	240
APACHE II	23 ± 10	21.0 ± 7.6	19.6 ± 7.0	22.5 ± 7	22.3 ± 7.1	29.0 ± 8.4	25.3 ± 7.9
Energy target	Weight, age, sex-based formula. Initial carbohydrate load 400 kcal/day 1, 800 kcal/day 2 in the early PN group	Harris Benedict equation for the study group, no target for the control group	25 kcal/kg BW/day	Indirect calorimetry or 25 kcal/kg corrected BW/day (women), 30 kcal/kg corrected BW/day (men)	Indirect calorimetry for study group, 25 kcal/kg BW/day (admission weight) for control group	Indirect calorimetry or Ireton-Jones Equation: 100 % EE for isocaloric group, 50 % EE for hypocaloric group	Adapted Harris Benedict equation: 100–90 % EE for target feeding group, 60–70 % EE for underfeeding group
Primary outcome	Shorter length of ICU stay and lower morbidity for late PN versus early PN	No difference in crude day-60 mortality in standard care versus early PN	No difference in infection and death (30 days) PN versus EN	Reduced nosocomial infections for EN + SPN versus EN	Lower hospital mortality for study group versus control group	Reduced infectious complications in isocaloric group	Lower (trend) 28-day all-cause mortality for permissive underfeeding versus target feeding
Limitations	Most patients without indication for nutrition. Large drop out rate. Overfeeding plus carbohydrate load	Rather low illness severity. Not blinded	Energy target not met in majority of patients. No control group. Low severity	Relatively small number of patients. Not blinded	Non-nutritional energy delivered not taken into account. Small number of patients	"isocaloric" group received only 75 % of target. No restrictions on route of feeding	Target feeding group received only 70 % of target. Single center, not blinded

EN enteral nutrition, *PN* parenteral nutrition, *EE* energy expenditure, *BW* body weight, *SPN* supplemental parenteral nutrition

Recently, an increased morbidity was associated with the generalized use of early PN without an indication for nutritional support [7] (Table 1). The most widespread conclusion has been that underfeeding for 7 days was desirable. Twenty years after the Veteran trial [8], it was again concluded in 2011 that PN was deleterious: It took time to understand that the Veteran trial showed that overfeeding—particularly by the parenteral route—in patients without an indication for nutritional support was deleterious; it will probably take many years before the EPaNIC trial is properly understood, and particularly that it again showed that overfeeding is a deleterious strategy. The interpretation of the results is the cornerstone for progression.

Fortunately, these results were soon after contradicted by two large randomized controlled trials (RCTs) [9, 10] showing a favorable outcome in patients with an indication for nutrition. The difference is partially explained by the avoidance of a carbohydrate load which prompts higher insulin requirements and inhibits autophagy [11] and the overfeeding [6]. Another study has shown that progressive increase of enteral feeds delivery up to an energy target measured by indirect calorimetry, intermittently supplemented by PN, reduces the risk of nosocomial infections [12]. Epke et al. [13] recently showed that an energy deficit during the first days in the ICU is associated with MRSA bloodstream infection in prolonged mechanically ventilated patients and suggested that limiting this energy deficit could optimize their prevention.

Adapting intakes to measured expenditure: a key to success

Only an observational trial [14] and three RCTs in ICU patients have based the energy target on indirect calorimetry [12, 15, 16]: all four trials reported clinical benefits. Petros et al. [16] prospectively tested hypocaloric (50 % of measured energy needs) versus isocaloric (100 % of measured energy needs) feeding in 100 patients with an indication for nutritional support during the first 7 days after ICU admission. They found that underfeeding resulted in (15 %) more nosocomial infections.

Equations fail in 70 % of patients and overestimate the energy needs [17]. This is especially true in overweight or obese sarcopenic patients, and after prolonged physical immobilization. The impact of low energy delivery was unintentionally tested in three recent prospective RCTs with equation-based targets, which showed a better outcome in the patients belonging to the control group (i.e., those without overfeeding) [7, 15, 18, 19]. In fact, these trials tested overfeeding versus isocaloric or modestly hypocaloric feeding. Furthermore, in these trials, energy contained in the glucose solution for drug administration or lipids from sedation (i.e., propofol) was not considered, although this represents up to 10–15 % of the total administered energy. To simulate the impact of predictive formula on the adequacy of feeding, we applied the prediction formula based on corrected ideal body weight, age, and gender which was used in a former trial [7] to recalculate the energy target in our own study [12]. We found that this formula compared to indirect calorimetry resulted in major unpredictable differences in individual targets (i.e,. ±1,000 kcal/day): The EPaNIC trial tested overfeeding, rather than the impact of different feeding regimen. This statement is further supported by the twofold higher insulin requirements in the overfed PN patients.

Several RCTs have aimed to evaluate the impact of pseudo-underfeeding on clinical outcome. Arabi et al. [18] randomized patients into a control group (90–100 % of calculated requirement) or an underfed group (60–70 % of calculated requirement). The analysis showed that patients in the control group received 1,200 kcal/day and 43 g/day of protein, whereas those in the underfeeding group received 1,099 kcal/day (i.e., −9 %) but 47 g/day (i.e., +10 %). Hospital mortality was (5 %) lower in the underfeeding groups, with no difference in terms of outcome (primary outcome)—an unsurprising conclusion considering that the two groups had similar levels of underfeeding.

Perspectives

Cell respiration consumes O_2 and generates CO_2. Energy expenditure can accurately be determined from these exchanges, except in cases of acute and significant changes of pH, or chest leakage [20]. Unfortunately the availability of indirect calorimeters is very limited. An international initiative supported by two academic societies (European Society of Intensive Care Medicine, ESICM; European Society for Parenteral and Enteral Nutrition, ESPEN) aims at developing an accurate, easy-to-use, and affordable calorimeter to promote a large use of this technique. No further important studies should be conducted until energy expenditure is used to base their targets and evaluate the impact of optimal feeding on clinical outcome.

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