Editorial on the original article entitled "Permissive underfeeding of standard enteral feeding in critically ill adults" published in the *New England Journal of Medicine* on June 18, 2015

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Abstract: On June 18, 2015, the *New England Journal of Medicine* published an article entitled "Permissive underfeeding of standard enteral feeding in critically ill adults", which reports the results of a study that examined the impact of prolonged nutritional energy restriction for critically ill patients. The study design was unique in the sense that patients in both groups received similar doses of protein during the intervention, while the non-protein energy intake was reduced in the intervention group. The study showed no differences in outcome between the two study groups. These results add to a growing body of high quality evidence against the dogmatic belief that full enteral or parenteral feeding should be given as early as possible during critical illness to prevent complications. Further research is now needed to address the question of the optimal timing to provide more nutritional support for the benefit of the patients, possibly guided by improved biomarkers that need to be developed and validated, and to investigate underlying mechanisms.

Keywords: Nutrition; critical illness; hypocaloric feeding; isonitrogenous; renal replacement therapy; autophagy

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For decades, clinicians took for granted that morbidity and mortality of critical illness can be prevented by providing nutritional support as soon as possible, up to a calculated or measured energy and protein target (1). This "early full feeding" paradigm was largely based on observational and pathophysiological studies, which revealed an association between the degree of energy and/or protein deficit, which accumulates rapidly during the days after onset of critical illness, and a higher risk of morbidity and/or mortality (2). These studies also suggested that 1-2 g of protein per kilogram ideal body weight may be required to achieve a positive nitrogen balance (3). However, whether a positive nitrogen balance translates into less lean tissue wasting and faster rehabilitation has never been thoroughly investigated.

During the past 10 years, this "early full feeding during critical illness" concept has been challenged by several large randomized controlled studies (RCT) (4). Cluster randomized trials assessing the impact of an optimized macronutrient delivery showed that more energy and protein intake did not improve clinical outcomes (5,6). Also, several RCT's revealed that providing hypocaloric instead of full feeding enterally or parenterally early during critical illness either did not change or even improved outcome (4). These unexpected results generated the hypothesis that although providing non-protein calories up to a certain target for energy is futile (7-10) or even harmful (11,12) early during critical illness, the early provision of amino-acids up to the recommended levels may be essential to prevent loss of lean body mass (13). Results from a pilot study ("Cal III" or "Arabi-1") suggested indeed that the restriction of non-protein calories while providing full protein intake might improve survival (14). The hypothesis was subsequently tested in the large PermiT RCT that compared restriction of non-protein calories with normal non-protein calories

provided via the enteral route in a context of isonitrogenous feeding (15).

The results of the PermiT trial were recently published in the *New England Journal of Medicine* (May 20, 2015). Patients in this multicenter study, which was conducted in seven ICUs in Saudi-Arabia, Lebanon and Canada, were randomized to receive enteral feeding with up to 40-60% of the calculated non-protein energy requirements or to standard enteral feeding up to 2 weeks in the ICU, while patients in both groups received about 1 g of protein per kilogram lean body mass per day. This RCT is unique by this isonitrogenous study design and by the relatively long duration—2 weeks—of the intervention window. Selectively reducing the non-protein calories in the enteral feeding while providing a high dose protein intake did not change patients' outcome, despite a very large difference in the amount of non-protein energy was delivered over the first 2 weeks of illness. Biochemical "nutritional markers" were also unaffected. There was a reduced need for renal replacement therapy in the patients who received the non-protein energy restriction, but this was a post-hoc clinical endpoint.

The PermiT investigators adhered well to high methodological standards which are mandatory to generate confident estimates of treatment effects (15,16). A complete consort diagram of screening and inclusion was provided in the on-line supplement, allocation concealment was adequate and allocation to the two study interventions was stratified for seven pre-specified subgroups. Moreover, the patients who were included in PermiT trial were those considered by most clinicians as those most likely to be affected by nutritional interventions. These comprised predominantly non-surgical admission diagnoses, many patients suffering from sepsis at inclusion, with a median ICU stay of about 10 days. There was excellent adherence to the study protocol and the primary endpoint, 90-day landmark mortality, was available for 99% of patients in the intention to treat analysis.

However, the study also suffered from important limitations.

The first limitation is the choice of the primary endpoint, 90-day landmark mortality, and the hypothesized effect-size. None of the high quality RCTs on nutritional interventions showed a difference in mortality (4). Mortality remains an important safety endpoint to detect unexpected harm (17), but there is very little biological rationale to support an effect of a small change in the enterally administered nutrition on mortality. Instead morbidity and rehabilitation may be more suitable as the endpoints for nutritional interventions (18). For example, the burden of ICU-acquired weakness has recently shown to have an impact on long-term patient-centered outcomes (19,20). Hence, the large postulated effect size in the PermiT trial, an 8% absolute reduction of 90-day mortality, based on the observations in the small pilot study, likely inflated the anticipated power of the RCT. For a smaller effect on mortality and for a reasonable effect on more biologically relevant morbidity endpoints, the study lacked the statistical power (15). The only robust conclusion that can be drawn from the PermiT trial is that the nutritional intervention that was studied did not bring about an 8% absolute reduction in 90-day mortality, but then again, this could not to be expected based on the available literature. The comparison of the morbidity endpoints in the two study arms revealed some better numbers for the group receiving the hypocaloric feeding, although the differences did not reach statistical significance. A particularly interesting subgroup appeared to be those patients with hyperglycemia upon randomization, who may have been more likely to benefit from feeding below energy target [see on-line appendix (15)].

Second, the high BMI of most patients in PermiT is a limitation for generalizability of the study results to more normal weight or underweight patient populations (15). However, until now, the few preplanned subgroup analyses in several interventional nutrition trials revealed that patients in different BMI categories respond similarly to enhanced or hypocaloric feeding (7,10,11).

Third, double blinding of RCTs that evaluate nutritional interventions during critical illness is virtually impossible and thus another accepted limitation (16).

Together, these study limitations suggest that the PermiT trial may not yet be the definitive study on the topic, and in fact could justify the need of another and larger RCT.

A more fundamental discussion focuses on the pathophysiologic basis of the PermiT trial, the underlying biology of the study hypothesis of this RCT. Why would restriction of non-protein energy while providing "normal" protein intake to ICU patients bring about a better clinical outcome? This is not really clear from the introduction provided in the manuscript. Theoretically, glucose and fatty acids provided in excess of the metabolic capacity of patients could easily be stored in the adipose tissue temporarily. However, no such pathway exists for amino-acids provided in excess of the anabolic capacity. The only way to deal with an excess of amino-acids is by elimination

through ureagenesis, which imposes a metabolic burden for the liver. In the condition of critical illness, an anabolic benefit of providing more amino-acids has never been shown convincingly. For example, recent detailed metabolic studies demonstrated that exogenous glutamine is unable to suppress glutamine release via catabolism of skeletal muscle during critical illness (21). Also, in two sub-studies of the EPaNIC trial, muscle wasting-assessed macroscopically with CT scanning and microscopically in biopsies—has shown to be entirely resistant to the administration of all-in-one parenteral nutrition (containing amino-acids, lipids and glucose) together with insulin (22,23). Ureagenesis, as the only escape route when amino-acids are administered in excess of the anabolic capacity of the patient, may at least partly explain the increased need for renal replacement therapy with early parenteral nutrition, as shown in the EPaNIC trial (24) and in another recently published trial, the Nephroprotective trial (25).

In the PermiT trial, no data on the effect on plasma urea were reported, but a post-hoc analysis revealed a reduced need for renal-replacement therapy with restriction of non-protein energy in the context of isonitrogenous enteral feeding (7.1% *vs.* 11.4%, P=0.04, uncorrected for multiple testing) (15). As the protein load was similar in both study groups, this effect, if not observed by chance, is likely not explained by an effect on ureagenesis but instead suggests a protective effect of restriction of glucose or lipids on the kidney. First, providing less nutritional glucose in a setting where blood glucose control is not done strictly lowered blood glucose levels in the PermiT trial, and hereby kidney damage may have been prevented in the intervention arm (26). Another explanatory mechanism may be that by restricting lipid intake, autophagy may be activated, which may have contributed to a better coping with illness-induced tubular cell damage (27). Indeed, insufficiently activated autophagy has been initially demonstrated in liver and muscle of critically ill patients (28). Administration of parenteral nutrition, particularly when enriched with either extra protein or extra lipids further suppressed autophagy and provoked organ damage in a rabbit model of critical illness (29). In addition, in this model, pharmacological autophagy activation has shown to improve kidney function (27). Also in the EPaNIC study, not providing early parenteral nutrition and hereby tolerating severe macronutrient restriction up to 1 week in ICU, has shown to activate autophagy in skeletal muscle and this autophagy activation explained the reduced incidence of ICU-acquired weakness (23). Obviously, direct quantification of autophagy markers in kidney or other vital organs in patients is ethically and technically challenging if not impossible. However, a recent animal experiment confirmed that the protective effect of macronutrient restriction on cardiac function after myocardial infarction is autophagy dependent (30). As the most powerful suppressors of autophagy are amino-acids, one may wonder whether in the PermiT trial, both study arms suffered similarly from the autophagy suppressive effect of that high dose of enterally administered protein, which rendered any restriction in glucose or lipids rather ineffective.

Indeed, the most interesting question that now emerges from the previous RCTs and from PermiT is whether or not providing amino-acids early during critical illness is harmful rather than beneficial. To address this burning question, an RCT should be done with randomization for the protein intake. However, in the face of all the negative recent trials, the likelihood that such a trial will be done is small. The PermiT RCT undoubtedly adds to the growing body of evidence challenging the earlier concept of benefit with early full feeding in critical illness, either via the enteral route or via parenteral nutrition (4). Consequently, early invasive or costly interventions aiming at quickly achieving up-to-target intake of energy or protein appear inappropriate. Also, studies evaluating the outcome benefit of altering the composition of artificial feeding, and of the dose of protein, should probably focus on the more chronic phase of critical illness, pragmatically at least beyond the first week in ICU. At some point after onset of critical illness, the catabolic consequences of prolonged underfeeding will have clinical implications.

What appears urgently needed are studies that aim at identifying reliable biomarkers to indicate the onset of recovery and thus the "readiness" of the body to handle and use the provided macronutrients for anabolism and rehabilitation (18). The PermiT study, together with the other recent RCTs on the topic, has opened a fascinating new track in the field of nutrition during critical illness, and the results of more studies are eagerly awaited.

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Footnote

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