

STUDY SUMMARY
Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults
PermiT Trial

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Objective: The purpose of this study was to determine if moderate calorie restriction with concurrent adequate protein provision would improve the outcomes in critically ill adults. The study was designed to compare hypocaloric feeding to full feeding, while providing identical amounts of protein. Primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality in the ICU, 28-day mortality, in-hospital mortality, 180-day mortality and serial SOFA scores. Tertiary outcomes included days free from mechanical ventilation, ICU-free days, hospital length of stay, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusion of packed red cells, ICU-associated infections, feeding intolerance and diarrhea.

Background: Meeting calorie and protein requirements has been recommended in an effort to attenuate malnutrition and protein catabolism, both of which are associated with increased morbidity and mortality. Randomized controlled trials (RCTs) and observational trials have shown no decrease in mortality when energy intake is augmented. Calorie restriction has been shown to be beneficial in some RCTs. Animal studies have shown protein refeeding, not calorie refeeding, restores mitochondrial function in the setting of malnutrition.

Materials and Methods: This was an unblinded, pragmatic, randomized, controlled trial of 894 critically ill patients conducted at seven tertiary care centers in Saudi Arabia and Canada from 2009-2014. Inclusion criteria included enteral feeding within 48 hours of ICU admission with anticipated ≥ 72 hour stay. Patients were excluded if receiving PN, high-dose vasopressors, burns, brain death, liver transplantation or expected six-month mortality $> 50\%$. Caloric requirements were assessed using the Penn State equation for mechanically ventilated patients with BMI < 30 ; Ireton Jones EE for mechanically ventilated patients with BMI > 30 and IJEE for spontaneously breathing patients for applicable patients with BMI > 30 . Caloric goal was 40-60% of calculated needs for permissive underfeeding group and 70-100% of calculated needs for standard feeding group. If feeding provision did not meet requirements on one day, target feeding was increased the following day to make up calories. Protein requirements were calculated at 1.2-1.5 gm/kg body weight/day. Beneprotein[®] was used to supplement protein in the permissive-underfeeding group every four hours. No single feeding protocol was mandated as part of the study, but target blood glucose levels of 80-180 mg/dL were set. Intervention was continued for up to 14 days, or until ICU discharge, initiation of oral feeding, or death.

Results:

- 894 patients: 448 in Permissive Underfeeding Group (PUF) and 446 in the Standard Feeding Group (SF). Average age 50; approximately 35% female; average BMI 29; 35% with diabetes; 75% medical and 3-4% surgical; 20-22% non-surgical trauma patients. Average APACHE II scores 21, SOFA 10, mechanical ventilation 96-97%; vasopressor therapy 55-57%; Albumin 2.8. Both groups were evenly matched.
- Daily caloric goal/delivery was 1036/835 for PUF and 1826/1299 for SF ($p < 0.001$). Daily protein goal/delivery, in grams, was 85/57 for PUF and 88/59 for SF, respectively.
 - Permissive underfeeding group received an average of 46% estimated calorie needs
 - Standard feeding group received an average of 71% of estimated calorie needs
 - Both groups received 0.7gm protein/kg body weight/day.
- On Day 1, standard polymeric feeding was used in 59.5% PUF and 54.1% SF patients; diabetic formula was used in approximately 20% of both PUF and SF and disease-specific formulas were used in 20.1% PUF and 25.9% SF patients.

- Average daily blood glucose was 162-260 mg/dL for PUF and 170-260 mg/dL for SF (p=0.04). Units insulin provided per day was 15±27 for PUF and 22±40 (p=0.02) for SF.
- Primary endpoint of 90-day mortality was 27.2% in PUF and 28.9% in SF. No significant differences were seen in secondary outcomes: mortality in ICU, in-hospital mortality, 28-day mortality, 180-day mortality or Kaplan-Meier survival estimates. No significant differences were seen in tertiary outcomes.
- Renal replacement therapy was required less frequently in the PUF group (7.1% vs 11.4% with p=0.04). Fluid balance was 490±1408 mL/day PUF versus 688± 1196 mL/day SF (p<0.001).

Discussion: Standard feeding goals in critically ill patients did not improve clinical outcomes. PUF was associated with lower blood glucose levels, reduced insulin requirements and similar clinical indexes of protein status, as compared to SF patients. Higher caloric intake may be associated with kidney injury, and possible mechanisms include renoprotective effects of caloric restriction, improved insulin sensitivity and reduced incidence of hyperglycemia. Higher fluid balance in the standard-feeding group may correlate with observed higher requirement for renal replacement therapy.

Conclusion: Permissive underfeeding with full protein intake was not associated with lower mortality than providing full caloric and protein feeding. Possible confounders include:

- Study group represented only 14% of the ICU admissions; two-thirds of patients came from one hospital
- Target caloric intake was not reached in some patients, including SF patients
- Blinding of intervention was not done
- Duration of study was fixed, therefore result of prolonged PUF vs SF is not clearly known
- Adherence to optional multivitamin supplementation was not monitored
- Study was powered to detect absolute risk reduction of 8% in 90-day mortality and small treatment effect cannot be ruled out