STUDY PROTOCOL

Resting Energy Expenditure, Nutritional Intake, and Postoperative Outcomes in Patients Undergoing Total or Partial Pancreatectomy for Pancreatic Tumors: A Prospective Observational Cohort Study

Acronym: FEED-REE

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Ethics approval: *Ethics Committee of Evangelismos General Hospital,*

Conducted in accordance with the Declaration of Helsinki.

Contents

Contents 2
1. Protocol Synopsis 3
2. Background and Rationale 3
3. Objectives 4
3.1 Primary objectives 4
3.2 Secondary objectives 4
4. Study Design 4
4.1 Feeding-route groups 4
5. Study Population 4
5.1 Study population description 4
5.2 Inclusion criteria 5
5.3 Exclusion criteria 5
6. Study Procedures 5
6.1 Indirect calorimetry 5
6.2 Estimation of energy requirements for comparison 5
6.3 Nutritional intake and feeding-route documentation 6
6.4 Anthropometry and body composition 6
6.5 Nutritional risk screening and biochemical markers 6
7. Outcome Measures 7
7.1 Primary outcomes 7
7.2 Secondary outcomes 7
8. Schedule of Assessments 7
9. Statistical Analysis (Summary) 8
10. Data Management 8
11. Ethics and Informed Consent 8
12. Data Sharing 8
13. Anticipated Limitations 9
14. Selected References 9

1. Protocol Synopsis

Title	Resting Energy Expenditure, Nutritional Intake, and Postoperative Outcomes in Patients Undergoing Total or Partial Pancreatectomy for Pancreatic Tumors
Acronym	FEED-REE
Design	Single-center, prospective, observational cohort study
Population	Adults undergoing total or partial pancreatectomy for a pancreatic tumor
Primary aim	To measure resting energy expenditure by indirect calorimetry and assess the accuracy of predictive equations and weight-based targets against it
Secondary aims	To characterize postoperative nutritional intake by feeding route and its relationship to complications, readmission, mortality, and change in body weight/BMI
Enrollment (target)	*[insert target N]*
Setting	Surgery Unit, Evangelismos General Hospital, Athens, Greece
Follow-up	Preoperative baseline, early postoperative period, discharge, and 3–6 months after discharge

2. Background and Rationale

Patients undergoing pancreatic resection experience substantial surgical stress and systemic inflammation and frequently develop exocrine and endocrine pancreatic insufficiency. Together these place them at high risk of postoperative malnutrition, progressive weight loss, delayed recovery, and increased morbidity. Malnutrition and elevated energy expenditure, although they often coexist in this population, are conceptually distinct: malnutrition reflects a deficit in nutritional status arising from reduced intake, malabsorption, and tissue depletion, whereas resting energy expenditure (REE) reflects the metabolic response to surgical stress and inflammation.

No procedure-specific nutritional guidelines currently exist for pancreatic resection, and clinical practice varies widely across institutions. In the absence of direct measurement, clinicians rely on predictive equations (such as Harris–Benedict and Schofield) and on simplified weight-based targets (25–30 kcal/kg) recommended for surgical and oncology patients. The accuracy of these methods in this specific population is poorly characterized, and the degree to which the route and adequacy of postoperative feeding influence recovery has not been examined alongside directly measured energy expenditure within the same cohort.

Prior work at the same center provides direct rationale for examining feeding route. In an earlier prospective observational cohort of 82 patients undergoing pancreaticoduodenectomy, the route of postoperative nutrition was associated with distinct complication profiles: enteral feeding with oral intake was associated with fewer infectious complications, whereas parenteral feeding was associated with fewer gastrointestinal symptoms and complications, and no single route proved optimal on every measure. Critically, and irrespective of route, patients with the largest cumulative energy and protein deficits experienced significantly higher rates of overall complications, hospital readmission at 90 days and 6 months, and mortality at 30, 90, and 180 days than patients with smaller deficits. These findings indicate that the adequacy of energy and protein delivery — more than the feeding route itself — drives postoperative course, and they motivate integrating directly measured energy expenditure with prospective documentation of feeding route and intake adequacy in the same cohort.

This study is designed to address both questions in a single prospective cohort, pairing indirect-calorimetry measurement of REE with structured documentation of nutritional delivery and clinical outcomes, in order to provide primary data for the development of individualized nutritional support protocols in this high-risk surgical group.

3. Objectives

3.1 Primary objectives

- To determine measured resting energy expenditure (mREE) by indirect calorimetry during the early postoperative period.
- To assess the agreement and accuracy of predictive equations (Harris–Benedict, Schofield) and weight-based targets (25 and 30 kcal/kg of ideal body weight) against mREE.

3.2 Secondary objectives

- To quantify postoperative energy and protein intake relative to requirements, overall and by feeding route.
- To describe postoperative complications, hospital readmission, mortality, and change in body weight and BMI, and their relationship to energy and protein adequacy.
- To identify independent predictors of mREE.

4. Study Design

This is a single-center, prospective, observational cohort study. Consecutive eligible adults undergoing total or partial pancreatectomy for a pancreatic tumor are enrolled preoperatively after informed consent. The route of postoperative nutrition is not assigned by the study; it is determined case by case by the treating surgical and nutrition support teams according to clinical status and tolerance, and is recorded as an observed exposure. All measurements and data abstraction are performed by trained clinical dietitians, using direct measurement and the medical record.

Observational model: Cohort. **Time perspective:** Prospective. **Sampling method:** Non-probability (consecutive) sample.

4.1 Feeding-route groups

Within the single prospective cohort, participants are classified by their observed postoperative feeding route into three groups for planned comparison:

- Group 1 — Enteral nutrition with oral intake
- Group 2 — Parenteral nutrition only
- Group 3 — Combined enteral and parenteral nutrition

Feeding route is determined by the treating surgical and nutrition support teams on clinical grounds and is not randomized. These groups are therefore analytic strata of an observational exposure rather than assigned intervention arms, and comparisons across them are interpreted accordingly, with attention to confounding by indication.

5. Study Population

5.1 Study population description

Consecutive adult patients admitted for total or partial pancreatectomy — including pancreaticoduodenectomy (Whipple procedure) and distal pancreatectomy — for a pancreatic tumor at the participating center. The cohort reflects the real-world case mix referred for pancreatic resection and therefore includes both malignant tumors and premalignant or benign lesions (such as intraductal papillary mucinous neoplasm and ampullary tumors), spanning the head, body, and tail of the pancreas.

5.2 Inclusion criteria

- Age 18 years or older
- Scheduled to undergo total or partial pancreatectomy (pancreaticoduodenectomy/Whipple procedure or distal pancreatectomy) for a pancreatic tumor
- Able to complete indirect calorimetry measurement by canopy or face mask for the required duration
- Able to provide written informed consent

5.3 Exclusion criteria

- Age under 18 years
- Pregnancy
- Inability to tolerate the calorimetry canopy or mask for the duration required for a valid measurement
- Unable or unwilling to provide informed consent

6. Study Procedures

6.1 Indirect calorimetry

Measured resting energy expenditure is determined using a Cosmed Q-NRG+ portable indirect calorimeter, calibrated before each session according to the manufacturer's automatic gas-calibration procedure. Measurements are obtained by canopy where feasible, with a face mask used only when a canopy cannot be applied, recording oxygen consumption (VO_2) and carbon dioxide production (VCO_2).

Patients are measured supine, awake, and motionless in the morning after an 8–10 hour fast, at a controlled room temperature of 22–24 °C, following a minimum of 20–30 minutes of rest. The first five minutes of each recording are discarded, and steady state is defined as at least five consecutive minutes during which the coefficient of variation in VO_2 and VCO_2 does not exceed 10%. Caffeine and strenuous physical activity are avoided for at least 12 hours beforehand, and supplemental oxygen therapy is suspended or accounted for where clinically feasible.

mREE is derived using the abbreviated Weir equation: $mREE = (3.94 \times VO_2 + 1.11 \times VCO_2) \times 1.44$. The respiratory quotient is calculated as VCO_2 / VO_2. To reduce the influence of single-timepoint sampling within a dynamic postoperative course, calorimetry is scheduled at more than one time point during the early recovery period where the patient's clinical stability permits, and the exact days are recorded.

6.2 Estimation of energy requirements for comparison

Predicted resting energy expenditure is calculated for each patient using the Harris–Benedict and Schofield equations. For overweight patients, ideal body weight is used in these equations; for obese patients, corrected weight [ideal body weight + 0.25 × (actual weight − ideal body weight)] is used. Total energy requirements are additionally estimated from the ESPEN weight-based targets of 25 and 30 kcal/kg of ideal

body weight (adjusted using a BMI of 22 kg/m² for overweight and 24.9 kg/m² for obese patients) and compared with mREE adjusted by an activity/stress factor of 1.15.

Because the two families of estimates target different quantities — basal/resting expenditure for the equations versus total requirements for the weight-based targets — equation comparisons use raw mREE while weight-based comparisons use mREE × 1.15. This distinction is retained throughout the analysis, and error metrics are not treated as directly comparable across the two groups of methods.

Harris–Benedict equation

- Men: pREE = 66.47 + 13.75 × weight (kg) + 5.0 × height (cm) − 6.75 × age (years)
- Women: pREE = 665.09 + 9.56 × weight (kg) + 1.84 × height (cm) − 4.67 × age (years)

Schofield equation (by sex and age band)

- Men 30–59 y: 11.472 × weight (kg) + 873.1; Men ≥60 y: 11.711 × weight (kg) + 587.7
- Women 30–59 y: 8.126 × weight (kg) + 845.6; Women ≥60 y: 9.082 × weight (kg) + 658.5

6.3 Nutritional intake and feeding-route documentation

For each patient, the route of postoperative nutrition (enteral plus oral, parenteral only, or combined enteral and parenteral) is recorded, together with the formulation used, the daily administered volume, and the delivery rate. Daily energy and protein delivery are quantified against individually calculated requirements, which are derived from the ESPEN recommendations for surgical patients using ideal body weight. Diet-related symptoms (including diarrhea and abdominal pain) are recorded prospectively.

Cumulative energy and protein deficits are calculated as the difference between estimated requirements and actual delivery across the early postoperative period. For outcome analysis, patients are stratified into higher- and lower-deficit groups (dichotomized at the cohort median), enabling comparison of clinical outcomes by adequacy of intake in addition to comparison by feeding route.

Feeding-related postoperative complications are recorded using standardized definitions: delayed gastric emptying (DGE) and postoperative pancreatic fistula (POPF) are graded according to the International Study Group of Pancreatic Surgery (ISGPS) criteri*]*, and infectious complications and readmissions are recorded per institutional criteria. These data support the planned comparisons across the three feeding-route groups and across energy- and protein-deficit strata.

6.4 Anthropometry and body composition

Body weight is measured on a calibrated electronic scale to the nearest 0.1 kg. Height is measured with the patient standing upright, unshod and bare-headed, using the Frankfort horizontal plane for head alignment. BMI is calculated as weight (kg) divided by height squared (m²). Weight and BMI are recorded at the preoperative assessment, at discharge, and at the 3–6 month follow-up, and recent percentage weight change is documented. Because early postoperative weight is confounded by fluid shifts, third-spacing, and edema, preoperative weight is used as the reference exposure in modeling. Where available, objective body composition assessment (bioelectrical impedance analysis or CT-derived skeletal muscle measurement) is incorporated to distinguish loss of fat mass from loss of lean mass.

6.5 Nutritional risk screening and biochemical markers

Preoperative nutritional risk is screened using the Perioperative Nutrition Screen (PONS), which weights recent weight loss, reduced intake or anorexia, low BMI, and the presence of a high-metabolic-risk underlying disease. Serum albumin (as a surrogate marker of visceral protein status) and C-reactive protein (as a marker of systemic inflammation) are recorded as exploratory variables at defined time points around

the calorimetry measurement, per the hospital's standard laboratory procedures. Clinical variables — comorbidities, tumor site and surgical procedure, postoperative complications, length of stay, and readmissions — are abstracted from the medical record.

7. Outcome Measures

7.1 Primary outcomes

Outcome	Description	Time frame
Measured resting energy expenditure (mREE)	REE by indirect calorimetry, derived via the Weir equation (kcal/day)	Within 14 days after surgery
Agreement of estimation methods vs mREE	Bland–Altman bias and 95% limits of agreement, MAPE, and RMSE for Harris–Benedict, Schofield, 25 and 30 kcal/kg	Within 14 days after surgery

7.2 Secondary outcomes

Outcome	Description	Time frame
Energy and protein intake vs requirements	Daily delivery as % of calculated requirements, overall and by feeding route	First postoperative days through discharge
Respiratory quotient (RQ)	VCO_2/VO_2 as indicator of substrate utilization	Within 14 days after surgery
Postoperative complications	Delayed gastric emptying, postoperative pancreatic fistula, infectious complications	Surgery through 90 days
Hospital readmission	Proportion readmitted after index discharge	90 days and 6 months
All-cause mortality	Proportion deceased from any cause	30, 90, and 180 days
Change in body weight	Weight (kg) and % change from preoperative value	Preoperative, discharge, 3–6 months
Change in BMI	BMI (kg/m^2) and change from preoperative value	Preoperative, discharge, 3–6 months
Length of hospital stay	Duration of index hospitalization (days)	Surgery through discharge (up to ~30 days)

8. Schedule of Assessments

Assessment	Preop	Early postop (≤14 d)	Discharge	3–6 mo
Informed consent	X			
Eligibility / demographics	X			
PONS screening	X			
Indirect calorimetry (mREE, RQ)		X		
Anthropometry (weight, BMI)	X		X	X
Body composition (where available)	X		X	X
Albumin, CRP	X	X		
Feeding route / intake documentation		X	X	

Assessment	Preop	Early postop (≤14 d)	Discharge	3–6 mo
Complications / length of stay		X	X	
Readmission / mortality				X

9. Statistical Analysis (Summary)

Full detail is provided in the separate Statistical Analysis Plan. Analyses will be conducted in Jamovi with two-tailed tests at a significance level of $\alpha = 0.05$. Distributional normality is assessed by the Shapiro–Wilk test; normally distributed continuous variables are summarized as mean (SD) and non-normal variables as median (interquartile range), with categorical variables as counts and percentages.

Agreement between mREE and each estimation method is evaluated by Bland–Altman analysis (mean bias, 95% limits of agreement, and tests for proportional bias), complemented by accuracy indices (percentage within ±10% and ±20%, MAPE, and RMSE) and by linear regression of estimates against mREE. Determinants of mREE are examined using multiple linear regression with prespecified adjustment sets. Changes across time points are analyzed with repeated-measures ANOVA or Friedman's test as appropriate, with pairwise comparisons; where repeated calorimetry measurements are obtained, longitudinal trajectories are analyzed using linear mixed-effects models.

Comparisons across the three feeding-route groups use the chi-square or Fisher exact test for categorical outcomes (complications, readmission, mortality) and one-way ANOVA or the Kruskal–Wallis test for continuous variables, according to distribution. The same outcomes are additionally compared between higher- and lower-deficit strata for energy and protein separately. Because feeding route and intake adequacy are clinically determined rather than randomized, these comparisons are interpreted as observational and potentially subject to confounding by indication; subgroup analyses, including by surgical type, are treated as exploratory. The single-center design and anticipated sample size are recognized as constraints on statistical power and generalizability.

10. Data Management

Study data are recorded on standardized case report forms and entered into a secure, access-controlled database. Each participant is assigned a unique study identifier; the linking key between study identifiers and patient records is stored separately and accessible only to authorized study personnel. Data are handled in accordance with the EU General Data Protection Regulation (GDPR) and institutional data-protection policy. Source documents are retained per institutional and regulatory requirements.

11. Ethics and Informed Consent

The study is conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Evangelismos General Hospital. Written informed consent is obtained from all participants before any study procedure. Participation is voluntary and participants may withdraw at any time without affecting their clinical care. The study does not alter existing clinical management; feeding route and all treatment decisions remain at the discretion of the treating teams.

12. Data Sharing

De-identified individual participant data underlying published results will be made available to qualified researchers whose proposed use has been approved by an independent review committee, subject to a signed data-access agreement and to approvals from the sponsoring institution and the ethics committee, and only to the extent permitted by participants' informed consent and applicable data-protection law. Data will be available beginning 6 months after publication of the primary results and ending 36 months after publication. The study protocol and statistical analysis plan are available as registered supporting documents.

13. Anticipated Limitations

- Single-center design and limited sample size constrain statistical power and generalizability.
- Feeding route is clinically assigned rather than randomized, so comparisons across routes are observational and subject to confounding by indication.
- The postoperative day of calorimetry may vary between patients within the 14-day window; repeated measurements are obtained where feasible to partially address this.
- Where body composition is not assessed, weight loss cannot be fully partitioned into fat and lean mass.
- Exocrine pancreatic insufficiency (e.g., enzyme replacement, steatorrhea, fecal elastase) may not be fully captured and may contribute to nutritional decline independently of energy expenditure.

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