Study Protocol and Statistical Analysis Plan

Official Title: KOBE Study: Adherence and Tolerability of Different Very Low-Calorie Ketogenic Diet (VLCKD) Protocols in Adults With Obesity or Complicated Overweight

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1. Background and Rationale

Very low-calorie ketogenic diets (VLCKD) are medically supervised dietary interventions characterized by a marked reduction in caloric and carbohydrate intake, inducing a state of nutritional ketosis. These diets are increasingly used in the management of obesity and obesity-related metabolic conditions, including type 2 diabetes mellitus and non-alcoholic fatty liver disease. Although VLCKD protocols are widely applied in clinical practice, they differ substantially in terms of protein sources, including natural foods, protein supplements, and commercially available meal replacements. The KOBE Study was designed to collect real-world data from routine clinical practice in order to compare different VLCKD protocols and generate evidence to support informed clinical decision-making.

2. Study Objectives

Primary Objective: To compare four VLCKD protocols with respect to dietary adherence, occurrence of adverse effects, dropout rate, and patient-reported satisfaction with the diet.

Secondary Objectives: To evaluate changes in anthropometric parameters, body composition, biochemical and metabolic parameters, and liver steatosis and fibrosis assessed by ultrasound and transient elastography.

3. Study Design

This is a single-center, prospective, observational study conducted within routine clinical care at a hospital-based clinical nutrition service. Participants are not randomized and select the VLCKD protocol according to personal preference after standardized counseling.

4. Study Population

Inclusion Criteria: Adults with obesity (BMI $\geq$ 30 kg/m²) or overweight (BMI 25.0–29.9 kg/m²) with non-alcoholic fatty liver disease and a previous unsuccessful hypocaloric diet.

Exclusion Criteria: Age < 18 years, pregnancy or breastfeeding, moderate to severe renal insufficiency, significant cardiovascular disease, severe liver disease, type 1 diabetes mellitus or advanced type 2 diabetes, eating disorders, major psychiatric conditions, or frail elderly status.

5. Observational Groups

All VLCKD protocols consist of three phases (ketogenic phase, reintroduction phase, maintenance phase). The four observational groups differ only in the protein sources used during the ketogenic phase.

6. Study Procedures and Assessments

Participants undergo scheduled medical and dietary visits as part of routine clinical care. Collected data include anthropometric measurements, body composition analysis by bioelectrical impedance, laboratory tests, liver ultrasound and transient elastography, capillary blood ketone monitoring, and validated patient-reported outcome questionnaires.

7. Study Duration and Follow-Up

The active dietary intervention lasts approximately 26 weeks, with an additional follow-up visit approximately three months after completion.

8. Statistical Analysis Plan

Sample Size: A minimum of 21 participants per observational group is planned, with a total sample size ranging from 84 to 200 participants.

Statistical Methods: Descriptive and comparative analyses using parametric or non-parametric methods. Propensity score methods will be applied to account for the non-randomized design.

9. Ethical Considerations

The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Written informed consent is obtained from all participants prior to data collection.

10. Data Management and Confidentiality

Study data are collected using a secure electronic data capture system. Participant confidentiality is maintained through coded identifiers.

11. Dissemination of Results

Study results will be made publicly available through ClinicalTrials.gov and may be published in peer-reviewed scientific journals.