The Impact of Semaglutide on Gut Microbiota in Obese Patients

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1. Research Background and Rationale

Obesity is a chronic disease characterized by excessive fat deposition, which increases the risk of hypertension, diabetes, non-alcoholic fatty liver disease, sleep apnea syndrome, coronary heart disease, and other conditions. Ultimately, it affects patients' life expectancy and raises healthcare costs, making it one of the most severe global public health issues [1]. Weight loss can significantly reduce the risk of obesity-related complications [2]. Lifestyle interventions are the first-line treatment for obesity management, but even with strict adherence, they typically result in only a 5–10% reduction in body weight, which is difficult to maintain long-term. There is an urgent need for the development of highly effective and safe weight-loss drugs.

Glucagon-like peptide-1 (GLP-1) receptor agonists, represented by semaglutide, have been approved for chronic weight management in obese patients [6–7]. Numerous studies have shown that semaglutide treatment significantly reduces body weight in obese patients with a good safety profile [7]. However, it is noteworthy that the weight-loss effects of semaglutide exhibit significant individual variability [4–5]. The STEP-5 trial found that semaglutide treatment resulted in an average weight loss of 15.2% in non-diabetic obese or overweight adults, but 23% of participants showed no significant weight reduction [4]. The recently published SELECT trial revealed that 32.2% of obese or overweight adults experienced no significant weight changes after using semaglutide [5].

The gut microbiota plays a crucial role in maintaining host physiology and homeostasis [8]. Our previous research demonstrated that metformin treatment reduces the abundance of Bacteroides fragilis and increases levels of glycoursodeoxycholic acid (GUDCA), thereby improving blood glucose and insulin resistance [9]. Time-restricted feeding was found to increase the abundance of Ruminococcus torques (R. torques), which produces 2-hydroxy-4-methylpentanoic

acid (HMP) to inhibit the intestinal hypoxia-inducible factor-2α (HIF-2α)-ceramide pathway, thereby ameliorating liver inflammation and fibrosis in mice [10]. Recent studies have shown that gut microbiota also modulates host responses to treatments, contributing to individual variability in drug efficacy [11]. J. Balaich et al. discovered that microbial-derived acarbose kinases specifically metabolize and deactivate acarbose, affecting its glucose-lowering effects [12]. Our team previously found that gut microbial dipeptidyl peptidase-4 (DPP4) enters intestinal tissues under conditions of intestinal barrier damage, degrading active host GLP-1 and inducing glucose intolerance. Host DPP4 inhibitors like sitagliptin cannot effectively inhibit microbial DPP4 activity, which is a major reason for the high variability in clinical responses to sitagliptin [13].

In our preliminary study, we performed fecal metagenomic sequencing on obese patients treated with semaglutide, matched for baseline gender, age, and body mass index (BMI), and observed significant differences in gut microbiota composition and abundance before and after treatment. Further experiments in a high-fat diet-induced obese mouse model revealed that antibiotic treatment enhanced the weight-loss effects of semaglutide. These findings suggest that gut microbiota modulates host responses to semaglutide treatment, although the specific mechanisms remain unclear.

This study aims to elucidate the impact of semaglutide on gut microbiota in obese patients and explore the development of targeted microbial enzyme therapies, providing new targets for overcoming semaglutide resistance in weight loss.

2. Research Objectives

This study will employ fecal metagenomic sequencing and multi-omics technologies, along with an in vitro bacterial strain screening platform, to investigate the effects of semaglutide on gut microbiota in obese patients and elucidate the underlying mechanisms. The goal is to identify novel targets for developing drugs to overcome semaglutide resistance in weight loss.

3. Research Methods

3.1 Study Setting and Population

Obese patients visiting the Department of Endocrinology at Beijing Chaoyang

Hospital, Capital Medical University, from April 2025 to April 2026 will be recruited based on the following inclusion and exclusion criteria:

Inclusion Criteria:

- Age 18–60 years;
- BMI ≥ 30 kg/m²;
- At least one self-reported unsuccessful attempt at lifestyle-based weight loss;
- Willingness to participate and signed informed consent.

Exclusion Criteria:

- Self-reported weight change >5% in the 3 months before screening;
- Use of any weight-loss medication in the 3 months before screening;
- Use of glucose-lowering drugs in the 3 months before screening, HbA1c ≥ 6.5%, or history of type 1 or type 2 diabetes;
- Use of immunosuppressants, steroids, antidiarrheals, antibiotics, probiotics, lipid-lowering drugs, or other gastrointestinal motility drugs in the 3 months before screening;
- History of endocrine-related overweight or obesity (e.g., Cushing's syndrome);
- Triglycerides ≥500 mg/dL (5.65 mmol/L) at screening;
- Clinically significant gastric emptying abnormalities (e.g., severe diabetic gastroparesis or gastric outlet obstruction), gastrointestinal diseases, or surgical history;
- Thyroid dysfunction;
- History of mental illness;
- Personal or family history of multiple endocrine neoplasia or medullary thyroid carcinoma, or calcitonin ≥6 pg/mL;
- Abnormal liver function at screening (ALT and/or AST >3× ULN);
- Abnormal renal function at screening (eGFR <60 mL/min/1.73 m²);
- History of cardiovascular disease;
- History of malignancy;
- Pregnancy or lactation;
- Other conditions deemed unsuitable for participation by the investigator.

3.2 Study Design

Recruitment:

A self-controlled cohort study design will be used to recruit obese patients from the Department of Endocrinology at Beijing Chaoyang Hospital from April 2025 to April 2026.

Treatment and Follow-up:

Eligible participants will receive subcutaneous semaglutide injections. The treatment follows a dose-escalation regimen to achieve steady-state plasma concentrations over 4–5 weeks: Start with 0.5 mg once weekly; Increase to 1.0 mg once weekly after 4 weeks; Further increase to 1.7 mg once weekly after another 4 weeks; Total treatment duration: 12 weeks.

Participants will visit the clinic every 4 weeks for follow-up assessments, including general condition, physical examinations, and laboratory tests. At the 12-week follow-up, venous blood will be collected for semaglutide plasma concentration analysis.

Outcome Measures:

Primary Outcome: Changes in gut microbiota composition (abundance and Shannon diversity index) from baseline to 12 weeks.

Secondary Outcomes: Changes in weight, BMI, waist circumference, hip circumference, and lipid profiles from baseline to 12 weeks.

3.3 Sample Size Calculation

A paired t-test will be used for pre-post comparisons. Based on prior studies, the standard deviation of paired differences (σd) is 1.2, the clinically meaningful minimal difference (Δ) is 1.0, $\alpha = 0.05$ (two-tailed), $Z_{1-\alpha/2} = 1.96$, $\beta = 0.1$ (Power = 90%), and $Z_{1-\beta} = 1.28$. The calculated sample size is 16, accounting for a 20% dropout rate and 30% redundancy in microbiome data. The final sample size is 40, with adjustments based on recruitment feasibility.

3.4 Data Collection

1) Anthropometric Data:

Height, weight, BMI, waist/hip circumference, blood pressure, etc., measured by

trained staff.

2) Urine and Fecal Samples:

Urine: Midstream samples collected for biochemical analysis and stored at -80°C.

Fecal: Fresh samples collected internally to avoid contamination, stored at -80°C for metagenomic sequencing. DNA extraction, sequencing (Illumina HiSeq 4000), and bioinformatics analysis will be performed.

3) Blood Samples:

Fasting venous blood for routine tests (glucose, insulin, HbA1c, lipids, etc.) and semaglutide concentration (LC-MS/MS).

3.5 Follow-up Schedule

Participants will be followed every 4 weeks for 12 weeks, with assessments including physical exams, lab tests, and safety monitoring.

3.6 Data Management and Statistical Analysis

Data Management:

Double-entry verification using Epidata, with logic checks and error correction before database locking.

Statistical Analysis:

SPSS for analysis.

Normal distribution: Mean ± SD (paired t-test); non-normal: Median (IQR) (Wilcoxon test).$P < 0.05$ considered statistically significant.

3.7 Bias Control

Strict adherence to inclusion/exclusion criteria, standardized data collection, and multivariate regression to adjust for confounders (age, sex, baseline BMI, diet).

4. Quality Control

Fecal sample collection: Avoid urine contamination, use sterile containers, store at -80°C.

Questionnaire integrity: Trained staff, regular audits.

Accurate measurements: Certified professionals, quality-controlled lab procedures.

5. Risk Assessment and Mitigation

Risks:

Blood draw: Syncope/hypoglycemia.

Semaglutide: GI discomfort, allergies.

Mitigation:

Emergency protocols for adverse events.

Dose escalation and monitoring to minimize risks.

6. Expected Outcomes

Elucidate semaglutide's impact on gut microbiota and mechanisms.

Identify targets for overcoming resistance.

Publish 2–3 high-impact papers; patent applications if biomarkers are discovered.

7. Timeline

Period	Tasks
2025.04–2025.09	Recruitment and follow-up
2025.10–2025.12	Data analysis
2026.01–2026.04	Manuscript preparation/submission

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