Patient Information and Informed Consent for Participation in a Clinical Trial:

Metabolic Outcome of Obese Subjects receiving Fecal Microbiota Transplantation of Lean versus Gastric Bypass Treated Subjects. A Pilot Study

In accordance with the latest guidelines, testing of stool transplants and donors also includes testing the stool donor for COVID-19 infection to ensure a maximum level of safety.

Dear patient,

We invite you to take part in the above-mentioned clinical trial. You will be informed about the details of the study in a comprehensive medical consultation.

Participation in this clinical study is voluntary and can be terminated by you at any time without stating any reason, without any disadvantages to you.

Clinical studies are essential to obtain reliable new medical research findings. However, an indispensable requirement for conducting this clinical study is that you sign this patient information as a declaration of consent. Please read the following text carefully as a supplementary information completing your medical consultation and do not hesitate to ask any questions. Discuss this if necessary with friends or relatives.

Please sign the consent form only if you:

- understood the procedure of the clinical trial entirely,
- you are ready to agree to participate, and
- are aware of your rights as a participant in this clinical trial.

The responsible ethics committee obtained approval for this clinical study, the patient information and the consent form.

1. What is the objective of the clinical study?

Some studies have shown that the microbiome, or the total of all bacteria in the intestine, has a strong influence on our eating behavior, body weight, and metabolism. The type, number, and composition of these bacteria differ between lean and overweight individuals. People differ in their gut microbiota composition. Current science suggests that a disrupted gut flora plays a significant role in the development of obesity, and thus, restoring of a healthy gut flora is necessary for a successful weight loss. Numerous studies have shown that gastric bypass surgery can restore this balance in the gut flora and may be responsible for a long-term weight loss success. However, such surgery is irreversible, it means a serious surgical procedure for the patient, and carries a certain risk of surgery, therefore it is only approved as a last therapeutic option.

The purpose of this clinical study is to test an alternative, non-surgical obesity treatment using fecal bacterial therapy, also known as fecal microbiota transplantation. Additionally, the study aims to investigate whether there are differences in the recipients' response after receiving gut bacteria from a lean donor versus a gastric bypass operated donor.

In fecal bacterial therapy, gut bacteria obtained from the filtered stool of a donor are transferred into the colon during a colonoscopy. Since a very high amount of bacteria living in the gut cannot be cultured outside of the body, this procedure aims to restore a disrupted gut flora.

2. Course of the clinical study

This clinical trial is being conducted at the Department of Internal Medicine, Medical University Graz. A total of 40 individuals will participate, with 30 individuals receiving bacterial therapy with stool transplantation and 10 individuals serving as donors for stool samples. Among the 10 donors, there are 5 lean individuals and 5 formerly overweight individuals who have successfully responded to gastric bypass surgery in the past.

The recipients of bacterial therapy are randomly assigned to one of three experimental groups: (1) Bacterial therapy with stool transplantation from lean donors; (2) Bacterial therapy with stool transplantation from formerly overweight individuals who have already been successfully treated with gastric bypass surgery; (3) Bacterial therapy with autologous stool transplantation (= control group).

The study is double-blind, randomized, and controlled. Randomized means that those individuals receiving stool transplantation (= recipients) are randomly assigned to one of the three experimental groups. Double-blind means that neither the recipients of bacterial therapy nor the treating physicians know which experimental group the participants belong to. Controlled means that a number of recipients are assigned to a control group, which receives bacterial therapy with autologous stool.

The total duration of the study per patient is approximately 28 weeks.

A further detailed analysis of the pseudonymized stool and blood samples (microbiome as well as gastrointestinal hormones) will be carried out in the research group of Prof. Wiebke Fenske (Department of Internal Medicine, Endocrinology and Diabetology, Gastroenterology and Hepatology, University Hospital Bergmannsheil Bochum, Germany).

In accordance with the latest guidelines, testing of stool transplants and donors also includes testing the stool donor for COVID-19 infection to ensure a maximum level of safety.

The following measures are carried out for study purposes:

2.1. First Study Visit and Screening Examination

The first study visit takes place over two consecutive days, during which you are requested to come to the study center fasted on both days (no food intake except water is allowed for 8 hours before the examination). During the first study visit, you will be randomly assigned to one of the three experimental groups.

First Day of the First Study Visit:

After you have been fully and comprehensively informed and have signed the informed consent form, the inclusion and exclusion criteria are checked, demographic data (age, weight, height, etc.) and current medical conditions with corresponding medication will be collected. Furthermore, a physical examination will be performed, which includes measuring blood pressure, heart rate, and body temperature. As part of the screening examination, a blood sample will be taken, the basal metabolic rate will be determined by measuring inhalation/exhalation while sitting (indirect calorimetry), an ultrasound examination of the liver will be conducted, a urine test strip is used, and for women of childbearing potential, a rapid pregnancy test will be additionally performed. You will also be asked to complete questionnaires regarding your dietary habits and to provide a stool sample.

Subsequently, a permanent venous catheter will be inserted into one forearm, and a blood sample will be taken. Following this, you will be provided with a standardized test meal, with blood samples taken at 15, 30, 60, 90, and 120 minutes to determine blood glucose, insulin, blood lipid levels, bile acids, and hormones of the digestive system. After the final blood sample, the venous catheter will be removed.

Following this, a measurement of body composition (percentage of fat tissue and fat-free mass (= bones, muscles, etc.) will be performed using Dual-Energy X-ray Absorptiometry (= DEXA). The radiation exposure involved in this procedure is very low and equivalent to only 1/10–1/100 of a normal X-ray.

As a preparation for the bacterial therapy via stool transplantation, a sigmoidoscopy (an examination procedure of the lower part of the large intestine) will be performed. During this procedure, 4 mucosal samples will be taken from the rectum and 4 samples from the sigmoid colon. These samples will be used for tissue examination (histological examination) and an examination for bacterial content (microbiological examination).

Afterwards, you will receive antibiotic pre-treatment for 3 days, which aims to reduce your own bacterial flora.

Second Day of the First Study Visit:

After the first day of the study visit was successfully completed, the intravenous glucose tolerance test will be performed on the second day of the first study visit. For this test, two venous cannulas will be placed in the veins of both forearms.

Through one of the venous cannulas, glucose at a dose of 0.3g/kg body weight will be infused, and blood samples will be taken through the second venous cannula. This part of the examination lasts approximately 1 hour.

Subsequently, your blood sugar level will be maintained at a constant level for two hours through continuous glucose/insulin infusion (clamp method[1]). For this purpose, blood will be drawn every

[1] A glucose clamp method is used for measuring insulin secretion and insulin resistance of a patient. This method helps to determine how effectively a patient can metabolize ingested glucose and how sensitive his organs response to insulin.

5-10 minutes from one of the forearm venous cannulas, and the blood glucose concentration will be determined, while glucose and insulin are infused into the vein of the other arm.

You will spend this part of the study visit lying in bed. However, you may leave the bed if needed. During the study, you can drink as much water as you like. After the examination is completed, the venous cannulas will be removed.

Due to the involvement of many "clinical areas," it may happen that individual examinations/therapies need to be conducted on days other than planned. These shifts always occur within the two visit days and have no influence on the outcome of the study.

2.2. Bacterial Therapy

After the antibiotic therapy is completed, the standard procedure of bowel emptying will be performed before a total of 300 - 500ml of filtered and diluted stool from a donor will be transferred into your colon during a complete colonoscopy (complete colon). The stool used for this purpose comes from a healthy individual who has been screened for chronic communicable diseases such as HIV, hepatitis, salmonella, etc. The stool is filtered in advance and diluted with saline solution, and the resulting suspension contains the gut bacteria. To ensure the colonization of bacteria on the intestinal mucosa, the administration of donor stool is repeated 2 additional times during a sigmoidoscopy (lower part of colon) as part of an outpatient visit within the next 2 weeks. You will be asked to bring a stool sample for examination each time.

2.3. Follow-up Visits

To assess your response to the therapy, a total of 3 follow-up appointments are scheduled, which take place 1, 3, and 6 months after the last bacterial therapy. You are asked to arrive fasted to these appointments. During the 3 follow-up appointments, the examinations will be the same as those conducted during the first study visit, spread over 2 days.

Day 1: Physical examination, blood draw, intake of a standardized test meal followed by blood draws, measurement of body composition, indirect calorimetry, sigmoidoscopy (colonoscopy) including the collection of 4 mucosal samples from the rectum and 4 samples from the sigmoid colon.

Day 2: Blood draw, intravenous glucose tolerance test, clamp procedure.

The follow-up visits, like the first study visit, take place over two consecutive days. Due to scheduling conflicts with other departments, there may be shifts in individual examinations/therapies. These shifts do not affect the outcome of the study.

3. What are the benefits of participating in this clinical trial?

For those who respond to this therapy, there may be an improvement in obesity, metabolic function (such as diabetogenic metabolic condition), and restoration of a healthy gut flora.

4. Are there risks, complaints, and side effects?

Risks associated with bacterial therapy:

Infectious diseases that could be transmitted through the donor's fecal matter are excluded in advance. No side effects were detected after a fecal bacterial therapy via colon in previous studies. There is no greater risk associated with the clinical study colonoscopy than with a routinely performed colonoscopy.

During the sigmoidoscopy and tissue biopsy, there is a very low risk (< 1 : 10,000 examinations) of injuring the colon, resulting in bleeding and possibly requiring a surgery. Sigmoidoscopy may cause discomfort and slight pain due to the blowing of air into the colon.

However, the long-term effects of fecal bacterial therapy, such as the transmission of unknown pathogens or the onset of various chronic diseases (including metabolic diseases, immune diseases, or tumors), are currently unknown and cannot be estimated based on current research.

Risks associated with blood draws:

Rarely, intravenous cannulas can cause a small bruise at the puncture site. Such bruises are harmless and typically disappear on their own. In rare cases, there may be inflammation or scarring at the puncture site.

The total amount of blood drawn across all study visits during the 28-week study duration is approximately 300-350 ml. In comparison, a blood donation typically involves the withdrawal of about 450 ml of blood at once. If you experience any issues and the investigator is concerned, you will be immediately excluded from the study.

A possible side effect associated with insulin administration is hypoglycemia (low blood sugar). This side effect can have a mild course and cause symptoms such as cold sweat, hunger, headache, nausea, mild hot flashes, heart palpitations (increased heart rate), dizziness, tremor, weakness, and concentration difficulties. In extremely rare cases, hypoglycemia can lead to loss of consciousness and coma. However, this is prevented by close monitoring of blood sugar levels and an appropriate adjustment of glucose infusion.

Insulin can also cause changes in your blood potassium level. For your safety, potassium measurements will be performed every hour, and potassium infusion will be administered if necessary.

5. Additional intake of medications?

The study investigator must be informed about the intake of any medications, as well as over-the-counter medications and herbal cures that you may be taking during the study period. If it becomes necessary to take new medication due to circumstances (emergencies), inform the study investigator or the responsible representative of the study staff immediately.

6. What to do in case of symptoms, side effects, and/or injuries?

If any symptoms, side effects, or injuries occur during the clinical study, you must inform your doctor. In case of severe side effects, communicate them immediately, optionally by phone (telephone numbers, etc. see below).

7. Insurance

A legally required non-fault insurance coverage (personal injury insurance according to § 47 Medical Devices Act) exists for you as a participant of this clinical trial. It covers all damages that may occur to your life or health as a result of the measures taken during the clinical trial, except for damages resulting from changes in the genetic material in germ line cells.

The insurance has been arranged for you by:

Wiener Städtische Versicherung
Schottenring 30
1010 Vienna
Austria

The insurance company is reachable at the telephone number: +43 (0)5-0350 under policy number 08-N811157. Upon request, you may inspect the insurance documents.

In case of damage event, you may contact the insurer directly ant claim on your own initiative. The insurance contract is applicable to the Austrian law and insurance claims are enforceable in Austria.

You may also contact the Patient Advocacy Services, Patient Representative Services, or Patient Ombudsman for assistance.

To avoid putting the insurance coverage at risk:

during the duration of the clinical trial, you may only undergo other medical treatment with the consent of your treating investigator (excepting emergencies). This also applies to the additional intake of medication or participation in another study.

you must promptly inform the treating investigator - or the above-mentioned insurance company of any damage to health that may have occurred as a result of the clinical trial.

you must do everything reasonable to clarify the cause, course, and consequences of the insurance event and to minimize the resulting damage. This may include authorizing your treating physicians to provide information requested by the insurer.

8. Information for women of childbearing potential – Pregnancy test

Pregnant and lactating women are NOT allowed to participate in this clinical trial. To exclude pregnancy, a urine pregnancy test will be conducted at the screening examination for women

of childbearing potential. If you become pregnant during the clinical trial or suspect that you have become pregnant, please inform your investigator immediately.

9. In what case will the clinical trial be finished prematurely?

You can withdraw your willingness to participate and exit the clinical trial at any time without stating any reason without any disadvantages to you.
However, it is also possible that your investigator decides to terminate your participation in the clinical trial prematurely, without previous obtaining of your consent. The reasons for this may be:

a) You are unable to meet the requirements of the clinical trial.

b) Your treating physician believes that further participation in the clinical trial is not in your best interest.

10. Data Protection

Regarding your data collected in the context of this clinical trial, it is essential to distinguish between:

- personally identifiable data which allow to directly identify you (e.g., name, date of birth, address...) and
- pseudonymized (encrypted) data, where your complete identity information is replaced by a code (e.g., a number).

The code is strictly separated from the encrypted data sets and it is only kept at your trial center. The investigator and other staff members at the trial center involved in the clinical trial or your medical care have access to your non-encrypted data. The data is protected against unauthorized access. Additionally, authorized representatives of the sponsor and agents of national and/or foreign health authorities, as well as the respective ethics committees, may have access to the non-encrypted data as far as necessary for the verification of the proper conduct of the clinical trial. These individuals are subjected to strict confidentiality obligations.
Disclosure of data, especially to the sponsor and its contractual partners, only occurs in encrypted form. Encrypted data is also used for any publications.
You can revoke your consent to the collection of your data at any time. After your revocation, no further data will be collected about you. However, data collected until the revocation may continue to be used within the scope of this clinical trial.
Furthermore, according to legal requirements, if it does not affect the conduct of the clinical trial, you have the right to access your collected data and the possibility of correction if you detect any errors.
You also have the right to lodge a complaint with the Austrian Data Protection Authority regarding the handling of your data (www.dsb.gv.at).
All individuals who have access to your encrypted and non-encrypted data are subjected to the Austrian Data Protection Act in its current version and the General Data Protection Regulation (GDPR).

Furthermore, the duration of storage of your data is regulated by law. If you have any questions regarding the handling of your data in this clinical trial, please contact your investigator first. He can forward your concerns to the individuals responsible for data protection at the sponsor or the trial center if necessary.

Email contacts of the Data Protection Officer of the Trial Center, Hospital Authority: datenschutz@medunigraz.at or datenschutz@kages.at

11. Are there any expenses for participants? Is there reimbursement or any rewards?

Your participation in this clinical trial will not cause any additional costs for you.
For your participation in this clinical trial, you will receive a compensation according to the following conditions: Upon completion of the entire study, you will receive €1000. This total amount consists of the following partial amounts:

First study visit: €100
Bacteriotherapy 1, 2, and 3 each: €100
Control appointment 1, 2, and 3 each: €200
In the event of premature termination of the study, you will receive a proportional compensation for the visits completed up to that time point.

12. Opportunity for further discussion of any questions

For any additional questions related to this clinical trial, your investigator team is available to assist you. They will also be happy to address any inquiries regarding your rights as a patient and participant in this clinical trial.

Contact persons:

Priv. Doz. Univ. Ass. Dr. Patrizia Kump
Clinical Department of Gastroenterology and Hepatology, Medical University of Graz
Contact Tel: 0316/ 385 13350

Univ. Prof. Dr. Christoph Högenauer
Clinical Department of Gastroenterology and Hepatology, Medical University of Graz
Contact Tel: 0316/ 385 13350

Assoc. Prof. Priv. Doz. Dr. Julia Mader
Clinical Department of Endocrinology and Diabetology, Medical University of Graz
Contact: Tel: 0316/ 385 72831

DGKP Michael Oberosler
Contact: 0316 385-26177

Endocrinology Ward Beds: (0316)-385-13804

24-hour hotline: 0680 128 51 20

Patient and Nursing Ombudsman of the Province of Styria:

House of Health, Friedrichgasse 9, 8010 Graz
Phone: 0316/877-3350
Fax: 0316/877-4823
Email: ppo@stmk.gv.at

13. Consent Form

I consent to participate in the clinical trial: "Metabolic Outcome of Obese Subjects receiving Fecal Microbiota Transplantation of Lean versus Gastric Bypass Treated Subjects."

I have been thoroughly and comprehensively informed about the clinical trial, potential burdens and risks, as well as about the essence, importance, and implication of this clinical study, the existing insurance, and the requirements arising for me. Additionally, I have read the text of this patient information and consent form, which consists of a total of 10 pages. Any questions I had were answered clearly and satisfactorily by the investigator. I have had sufficient time to make my decision, and I currently have no further questions.

I will comply with the medical orders necessary for the conduct of the clinical trial but reserve the right to revoke my voluntary participation at any time without any disadvantages for my further medical care.

I explicitly agree that my data collected as a part of this clinical trial will be used as described in the "Data Protection" section of this document.

I agree that my general practitioner, upon my request, will be informed about my participation in the study.

I have received a copy of this patient information and consent form. The original remains with the investigator.

To be filled out by the patient: I agree with all statements on this form and want to participate in the clinical study:	
Signature:	Date:
Name (block letters):	

To be filled out by the responsible investigator who conducted the explanation: With my signature, I confirm that the entire process of obtaining consent has been conducted before any study activity took place	
Signature:	Date:
Name (block letters):	