Jejuno-ileal and jejuno-colic diversion as a new bariatric method in the treatment of diabetes and obesity

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Abstract

Background: Obesity is a serious disease that leads significantly to worse global health. Bariatric-metabolic techniques are one of the methods for an effective obesity treatment.

Objective: Our study should confirm the hypothesis that jejuno-ileal diversion (JID) and jejuno-colic diversion (JCD) lead to weight and fat mass reduction, have a positive effect on endocrine-metabolic function, and increase the bile acid in blood serum. Furthermore, we expect that JKB leads to greater and longer positive changes in body composition and endocrine-metabolic function without a negative effect on patient life.

Methods: This is a prospective nonrandomised clinical trial. Study subjects who meet Inclusion criteria and baseline procedures undergo surgery: first 20 patients JID / next 20 patients JCD. The subject will have follow-up clinic visits specific to the study at Weeks 1, 2, and 3 and at Months 1, 2, 3, 6, 12, 18, 24, 30 and 36 after the original procedure. At each clinic visit, the subject will undergo a review of medical history, evaluation of adverse events, physical examination (including weight and girth measurements) and blood work (e.g., glycated hemoglobin - HbA1c). At specific intervals, the principal metabolic studies will be performed, including a mixed meal tolerance test. Upper gastrointestinal (GI) series radiographic studies will be performed at baseline and 14 days after the procedure, as well as at the discretion of the principal investigator, focusing on the patency of the anastomosis.

Results: Statistical analysis will be split into three parts such as continuous outcomes (unpaired t tests); binary outcomes (McNemar's test or Z tests); baseline demographic and clinical variables (standard approaches / t test versus a null hypothesis/repeated measures analysis of variance.

Conclusions: The study is consistent with the principles and guidelines of the Declaration of Helsinki and good clinical practice and has been approved by the Ethics Committee. The surgical side-to-side jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis without gastrectomy potentially represent a new class of therapy with minimising its attendant risks. Clinical Trial: ClinicalTrials.gov NCT06374368.

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Trial Registration

ClinicalTrials.gov NCT06374368.

[Keywords]

Obesity; type 2 diabetes; partial jejumo-ileal diversion; partial jejuno-colic diversion; side-to-side anastomosis; bariatric surgery; metabolic surgery.

[Introduction]

Backround

In the past two decades, obesity has become a serious global health problem. In countries of central and Eastern Europe, including the Czech Republic, the prevalence of obesity is an eminent issue in all epidemiological studies (1). The results of the latest large epidemiological study, conducted in the Czech Republic, reveal that 30 % of Czechs are overweight and 25% suffer from obesity (2).

There are several therapeutic approaches to reduce obesity. In most cases, the first choice is a lifestyle change that focusses on balanced dietary intake and physical activity. Pharmaceutical therapy, the main objectives of which are to support the change in dietary habits and prevent the decrease in basal metabolism, is another option. However, since the end of the 1990s, surgical treatment (bariatric/metabolic surgery) has proven to be the most effective obesity treatment (3). Unlike conservative treatment, which fails in more than 80% of patients in the long term, metabolic surgery results in long-term success in more than 80% of patients (4). It is the only treatment that produces long-term weight loss in morbidly obese patients (5).
The growing incidence of obesity and T2DM is globally widely recognized as one of the most challenging contemporary threats to public health (6). In 2010, the global prevalence of T2DM was estimated at 8.3% of the adult population and is projected to increase to 9.9% by 2030 (7). In the morbidly obese population, the prevalence of Type 2 diabetes is disproportionately higher (23%) (8), which makes treatment even more difficult. Uncontrolled diabetes leads to macrovascular and microvascular complications, including myocardial infarction, stroke, blindness, neuropathy (9), and renal failure in many patients. The current goal of medical treatment is to stop disease progression by reducing hyperglycemia, hypertension, dyslipidaemia, and other cardiovascular risk factors (10).
In general, conventional medical treatment of T2DM only partially achieves adequate glycemic control and reduction in cardiovascular risk. Despite improvements in pharmacotherapy, less than 50% of patients with moderate to severe T2DM actually achieve and maintain therapeutic thresholds, particularly for glycemic control (11). With the exception of agonists of the glucagon-like peptide 1 (GLP-1) receptor and inhibitors of dipeptidyl peptidase 4 (DPP-4), oral hypoglycemic agents and insulin therapy can result in weight gain, which may further impair metabolic control (12).
In comparison, metabolic surgeries involving patients with T2DM have shown an overall rate of hyperglycemia remission of up to 78% (3). Remission occurs in approximately 50% of patients who underwent laparoscopic adjustable gastric banding (LAGB), 80% of those who underwent Roux-en-Y gastric bypass (RYGB), and 95% of those who underwent bioliopancreatic diversion (BPD). RYGB and BPD are believed to exhibit higher rates of remission compared to LAGB because they involve the rerouting of food through the small bowel, which activates the mechanisms of diabetes remission independent of weight loss (13). However, the risks of bariatric surgery are not trivial and the rates of complication are as high as 23% (14).

Prior work

In an effort to replicate the durable results of metabolic surgery in metabolic disease while minimising its risks, Department of Obesity and metabolic syndrome, Human Motion Diagnostic Centre, University of Ostrava has developed two innovative surgical methods to perform a bowel-to-bowel anastomosis, similar to the type used in current metabolic surgeries. Methods include jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis. Side-to-side jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis provide two routes for ingested food. The new, shorter route has a malabsorptive effect similar to that seen in Roux en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) procedures which lead to weight loss. Furthermore, the delivery of nonabsorbed macronutrients to the distal ileum or transverse colon can enhance an effect of incretin and improve Type 2 Diabetes Mellitus (T2DM) parameters. However, the native route is also preserved, which theoretically reduces the risk of malnutrition, diarrhoea, and metabolic derangements seen in other metabolic surgeries. The side-to-side jejuno-ileal anastomosis was already tested in the pilot study of the GI Windows Self-Forming Magnetic (SFM) Anastomosis Device for Creation of an Incisionless Small Bowel Diversion for Treatment of Obesity and Diabetes in year 2015 (15).

Goal of this study

The results of this study demonstrated the safety of this approach without serious adverse events. This nonsurgical approach resulted in significant weight loss, favourable changes in insulin and incretin responses to a mixed meal, and significant improvement in HbA1c in T2DM (16). In summary, metabolic diseases are a growing pandemic with suboptimal clinical solutions. The surgical side-to-side jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis without gastrectomy potentially represent a new class of therapy that can produce durable clinical results generally associated with surgery while minimising its attendant risks.

Hypothesis

I. Jejuno-ileal and jejuno-colic anastomosis leads to weight and fat mass reduction at time points at 1, 3, 6, 12, 18, 24, 30 and 36 months
II. Jejuno-ileal and jejuno-colic anastomosis have a positive effect on endocrine-metabolic function such as HbA1c, lipids, and incretins
III. Jejuno-ileal and jejuno-colic anastomosis increase bile acid in blood serum
IV. Jejuno-colic anastomosis leads to greater and longer positive changes in body composition and endocrine-metabolic function without a negative effect on patient life.

Study endpoints

The primary endpoints in the study will be measured at 1, 3, 6, 12, 18, 24, 30 and 36 months:

I. Percent total body weight loss (change in body composition)
II. Decrease in glycated hemoglobin (HbA1c)
III. Reduction in diabetes medication requirements (for the diabetic cohort)
IV. Change in blood lipids (total cholesterol, LDL, triglycerides, HDL) among subjects with elevated baseline levels
V. Change in adipose tissue and GI-produced hormons (leptin, adiponectin, incretins) and cytokines among subjects with elevated baseline levels
VI. Change in bile acid concentration in blood

Secondary endpoints in the study, assessed at 1, 3, 6, 12, 24 and 36 months, are

I. Improvement in baseline quality of life as measured by IWQOL and SF-36

[Methods]

This is a prospective nonrandomised clinical trial aimed at assessing the changes in weight, presence of T2DM, inflammation and the representation of bile acids over the course of 36 months. In case the participant meets all the inclusion criteria and no exclusion criteria and the sign-in consent form will be enroled in the study. The first 20 participants will be assigned to the jejuno-ileal arm and the other 20 patients will be assigned to the jejuno-colic arm. Blinding of study groups is not possible due to a specific type of intervention. The patients will undergo the surgical procedure at the Centre of Bariatric Medicine, Hospital AGEL– Ostrava-Vitkovice, and study visits will be performed at the Human Movement Diagnostic Center at the University of Ostrava, Czech Republic.
A priori power analysis - Based on the results of our previous study on small bowel diversion and in light of other recent publications, we performed a sample size calculation (using Stata v.

17, StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Input criteria such as minimum expected difference (effect size), estimated measurement variability, desired statistical power 80%, significance criterion 5%, and whether a one-tailed statistical analysis was selected based on our previous publications. Considering the length of the study, the number of patients available for selection at the bariatric centre, and the effectiveness of using diagnostic kits, we expect that a study sample size of 40 persons should be enough to demonstrate differences between groups.
Enroled patients are prohibited to use drugs or additional medicinal products that lead to weight loss until study completion. Enroled patients are prohibited to undergo another bariatric procedure or plastic surgery until the study is complete.
Any reportable event experienced by the study subject after informed consent, before, during or subsequent to the procedure, will be recorded in the related source documents or case report forms.
Records and information created or obtained during the course of the study ('study data') will be processed, manually or electronically. Study data will be retained for as long as necessary for legitimate business purposes in accordance with the University of Ostrava record retention policy and relevant laws and regulations, including the General Data Protection Regulation (GDPR) - Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016.
The collected data will be processed under a specific patient code. The double data entry method will be used.
During the study, monitoring will be performed to assess continued compliance with the protocol and applicable regulations.
The results are expected to be published in professional journals according to the author policy of the University of Ostrava.

Recruitment

The target population will be patients with obesity with or without T2DM. Patients who meet the inclusion criteria without any exclusion criteria (Table 1) after face-to face evaluation will be offered to participate in the study. There will be 20 patients in each arm (40 in total).
Stratification will be performed on each arm: diabetic and non-diabetic patients 1 : 1.
The file size will be 40 patients who undergo surgery and complete the study protocol at the time of 36 months from surgical procedure. This nonrandomised clinical trial will include obese patients in two arms:
Arm 1: obese patients with jejuno-ileal diversion
Arm 2: obese patients with jejuno-colic diversion
Note: The first 20 patients will be assigned to the jejuno-ileal arm and the other 20 patients will be assigned to the jejuno-colic arm.

Table 1. Study inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
Age 18-65 years at screening	BMI >50 or <30
BMI ≥30 or ≤50	Diagnosis of T2DM less than 6 months

If subject has T2DM: fasting plasma glucose greater than 6,1 mmol/l at the time of enrolment if not treated with antidiabetic medication. If on no diabetes medications, HbA1c between and including 6.5 % and 9.0 % at the time of enrolment.	History of or suspected gastrointestinal disease (e.g. cirrhosis, inflammatory bowel disease)
	History of active malignancy (i.e., not in remission) with the exception of squamous or basal cell carcinoma of the skin
	Ongoing systemic infection
	Chronic pancreatitis
	Chronic liver disease of any cause
	Poorly controlled psychiatric disease (e.g., ongoing major depression, schizophrenia, borderline personality, suicidality, psychosis)
	Any history of eating disorder within the past 5 years
	Pre-existing severe comorbid cardiorespiratory disease (e.g. congestive heart failure, cardiac arrhythmia, coronary artery disease, chronic obstructive lung disease, pulmonary embolism)
	Uncontrolled hypertension (systolic BP > 150 mm Hg or diastolic BP > 100 mm Hg)

Study Design

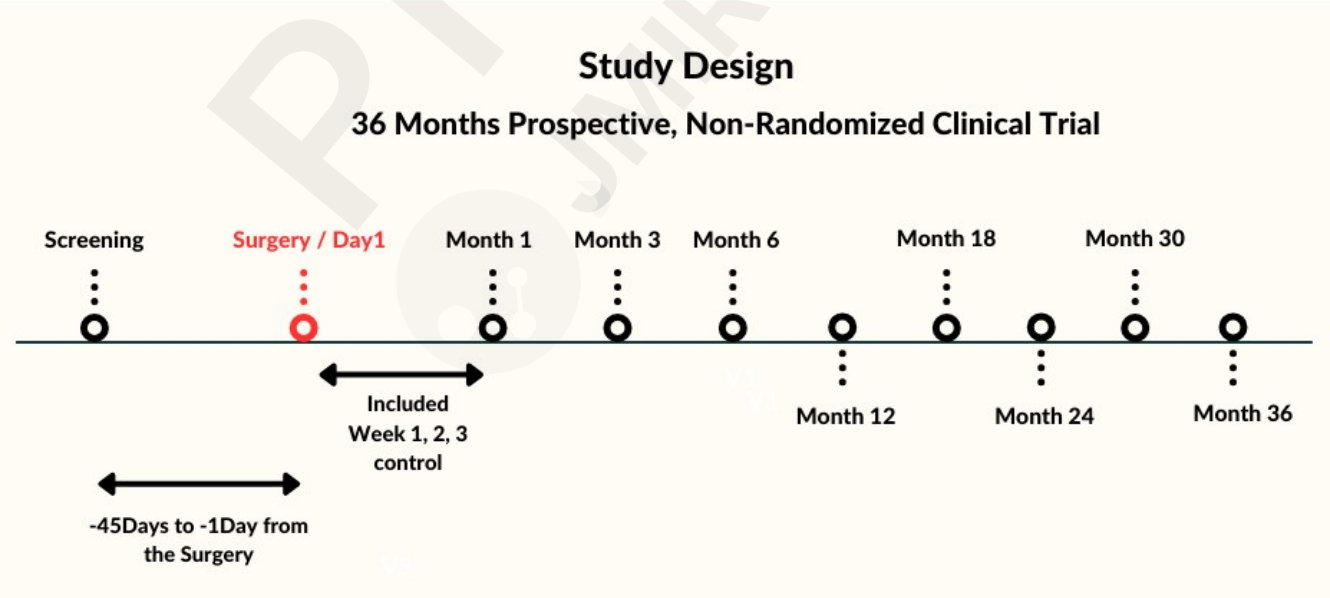


Figure 1. Study design - Timeline of interventions and follow-up of participants enroled in the study *(created by Canva.cz)*

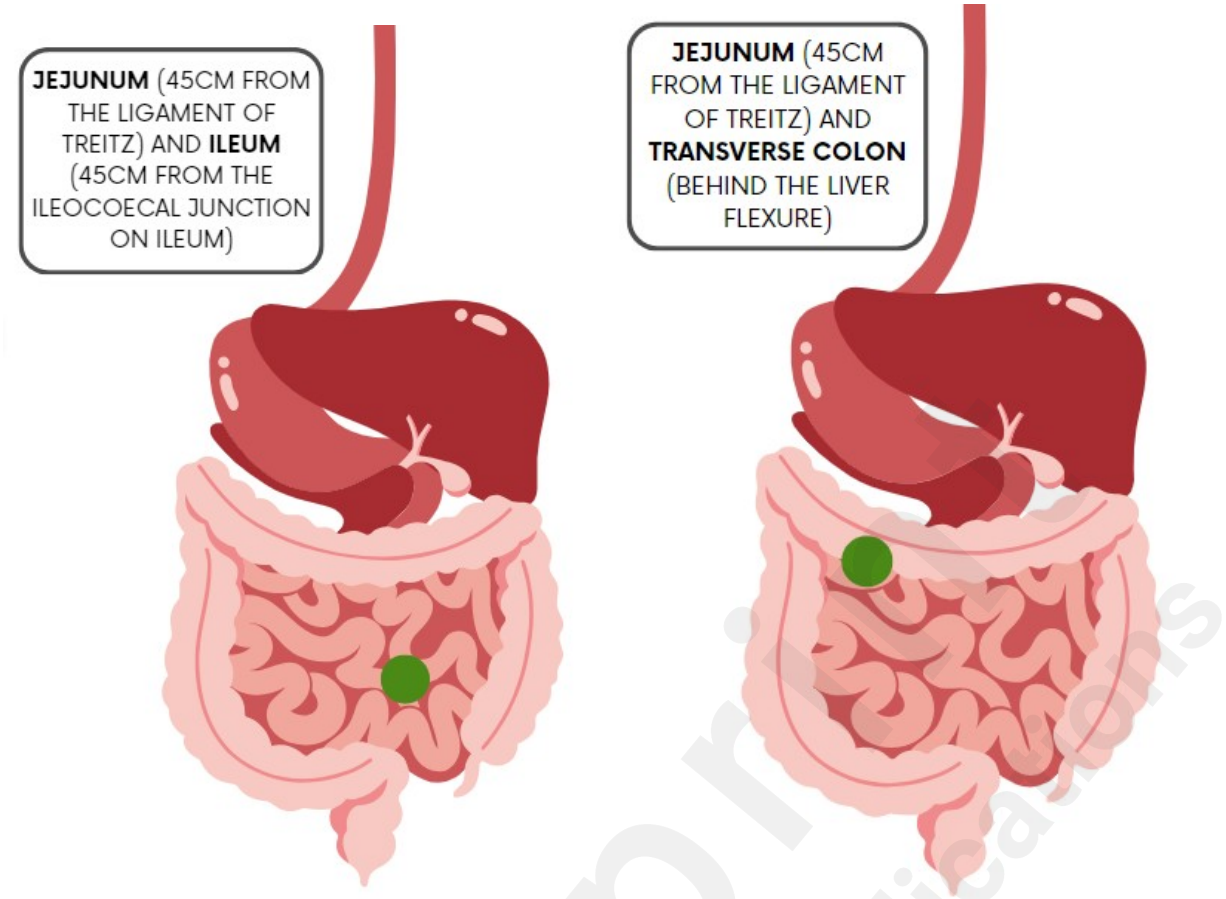
Informed consent process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or the legally authorized representative and answer all questions regarding the study.
Participants must be informed that their participation is voluntary. Participants or their legally authorised representatives will be required to sign a statement of informed consent that meets the Declaration of Helsinki, local regulations, International Council for Harmonisation (ICH) guidelines, privacy and data protection requirements, where applicable, and the Institutional Review Board (IRB) / Independent Ethics Committees (IEC) or study centre.
The medical record must include a statement that written informed consent was obtained before the participant was entered into the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the informed consent form.
A ditto of the inform consent form must be provided to the participant or the legally authorized representative and kept on file.
If the protocol or informed consent is updated, the patient will be informed in the form of an updated informed consent.

Surgical procedures: Jejuno-ileal diversion, Jejuno-colic diversion

Study subjects who meet Inclusion criteria (Table 1) and baseline procedures undergo surgery (jejuno-ileal diversion / jejuno-colic diversion). Surgery is performed under general anesthesia with orotracheal intubation. The laparoscopic approach is used. After establishing pneumoperitoneum (insufflation of the abdominal cavity with CO2), the first trocar and laparoscopic camera are introduced through a small incision. After visual control of abdominal cavity, additional 2-3 trocars for operating instruments are introduced. The site of future anastomosis is identified (45 cm from the Treitz ligament on jejunum and 45 cm from the ileocoecal junction on ileum).
The anastomosis between these two parts of the jejunum and ileum is created by means of linear stapler (45 mm) for patients in the first group (jejuno-ileal diversion, Figure 2 - left). The residual defect is closed with continuous manual suture. The food will pass through the intestine partially through whole small intestine and partially through anastomosis.
In the second group (jejuno-colic diversion, Figure 2 - right) of the patients, the anastomosis created between the jejunum (45 from the Treitz ligament) and the transverse colon (behind the liver flexure) is created by the same technique.
Before the end of the operation, bleeding control is performed. Subsequently, the trocars are removed under visual control. The pneumoperitoneum is released and the incisions are sutured.

Figure 2. Model of jejuno-ileal diversion (left) and jejuno-colic diversion (right); (created by Canva.cz).



Follow-up evaluations

During the follow-up period, patients enroled in the study will be monitored by a multidisciplinary team that includes bariatric surgeons, endocrinologists, nutritionists, psychologists.
Subjects will have follow-up clinic visits specific to the study at weeks 1, 2, and 3 and at months 1, 2, 3, 6, 12, 18, 24, 30 and 36 after the original procedure (Figure 1). At each clinic visit, subjects will undergo review of medical history, an evaluation of adverse events, physical examination (including weight and girth measurements), and blood work (e.g. HbA1c). At specific intervals, the principal metabolic studies will be performed, including a mixed meal tolerance test. Radiographic studies of the upper GI series will be performed according to the schedule outlined in Table 2, as well as at the discretion of the principal investigator, focusing on the patency of the anastomosis.

Description and justification of chosen methods and approaches

Description of the interventional therapeutic procedures proposed (Table 2):
Medical history. At the first visit (baseline), the investigator or coordinator will record details of the medical and surgical history related to diabetes and prior treatment, including assessment of hypoglycemia. Following the procedure, the medical history will also include a review of general well-being and gastrointestinal symptoms. At each visit, the investigator recorded details of the medical and surgical history and their changes.

Medication review. Each medication taken on a regular basis will be recorded at baseline and in all follow-up assessments. The specific dosage for diabetes medications will be recorded. Medications will be adjusted at each visit by the study physician according to the results of the home blood glucose monitoring, the appearance / frequency of hypoglycemia, and in-clinic laboratory results.

Blood pressure. Blood pressure will be recorded using a sphygmomanometer with the subject sitting at rest for at least 5 minutes. Three separate recordings will be taken, and the median (middle) value measurement will be recorded. Blood pressure will be evaluated at baseline and in all follow-up evaluations.

Height. Height will be recorded in centimetres at the baseline visit only.

Weight. Weight will be recorded in kilogrammes using a standard scale. The scale should undergo calibration on a regular basis according to the site's standard procedures. The site will use the same scale for each weight measurement in the study. Weight should be recorded in undergarments only, with jewellery and shoes off. Weight will be obtained at baseline and all follow-up assessments.

Measurement of girth (waist and hip). Girth measurement will be recorded in centimetres at baseline and all follow-up assessments.

DXA (dual-emission X-ray absorptiometry). Body composition will be assessed in all participants using the DXA (Discovery A; Hologic, Waltham, MA, USA). The following parameters will be monitored: fat body mass (kg), fat body mass (%), estimated visceral adipose area (EST VAT, cm^2), lean body mass (LBM, kg). The densitometer will be calibrated according to the manufacturer´s recommendations and the precision of the instrument will be established. DXA must be obtained at baseline and all follow-up assessments.

Labs. Blood will be drawn and undergo standard laboratory tests for the following (baseline, months 1, 2, 3, 6, 12, 18, 24, 30 and 36):

Biochemical analysis – included glucose, liver function tests (ALT- Alanine aminotransferase, AST- Aspartate amino transferase, total bilirubin, ALP-Alkaline phosphatase, GGT-Gammaglutamyltransferase),TSH, HCG (premenopausal women), total cholesterol, LDL, HDL, triglycerides, total calcium, magnesium, iron, ferritin, folate, phosphate, parathyroid hormone, total protein, albumin, creatinine, vitamin A, vitamin B1, vitamin B6, vitamin B12, vitamin C, vitamin D, urinalysis , spot urine albumin/creatinine ratio

Complete blood count (CBC) – included hemoglobin, hematocrit, WBC, platelets

HbA1c

Incretins (C-peptide, Insulin, GLP-1, Ghrelin Active, GIP, PYY); Myokines (FGF21, FGF19, Spexin), Following parameters (C5a, CD40 ligand, G-CSF, GM-CSF, CXCL1, CCL1, ICAM-1, IFNgamma, IL-1 alpha, IL-1 beta, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-16, IL-17, IL-17E, IL-18, IL-21, IL-27, IL-32 alpha, IP-10, I-TAC, MCP-1, MIF, MIP-1 alpha/beta, CCL5, SDF-1, PAI-1, TNF alpha, TREM-1)

To reduce analytical variation, hormones and cytokines produced by adipose tissue and gastrointestinal of all patients will be analysed in the same run. Blood samples will be stored at -80° C until the time of analysis. Values will be characterised as normal or abnormal based on the basis of local laboratory standards. If the values are abnormal, the investigator will indicate whether the abnormal value is clinically significant or not.

Mixed meal tolerance test. A mixed meal tolerance test will be performed after ingestion of Fresubin (or equivalent liquid). Samples will be obtained at -15, 0, 5, 15, 30, 60, 90, and 120 minutes for C-peptide, insulin, GLP-1, Ghrelin Active, GIP, PYY and glucose. Two duplicate cryotubes will be obtained for every time point and stored. Mixed meal tolerance test and metabolic studies are planned to be performed at baseline visit and at months 2, 6, 12, 18 and 24.

Upper GI series (with small bowel follow-through). Subjects will ingest radioopaque liquid contrast (e.g. Gastrografin) and X-rays obtained to document anastomosis patency and presence/absence of leak. This study will be obtained within 45 days prior to the procedure, 2 weeks after treatment, and as clinically indicated based on the discretion of the investigator.

Endoscopy. Subjects will undergo endoscopy or colonoscopy to examine the anastomosis at months 2 and 12.

Behavioural and dietary counseling. Behavioural screening/counseling will be obtained prior to enrolment. Dietary counseling will be provided at regular intervals (baseline, months 1, 3, 6, 12, 18, 24, 30 and 36). Note that case report forms collect only attendance at such programmes, not the content of the programme. In these programmes, no study-related assessment is performed beyond noting attendance. Subjects will be advised to follow a regimen of routine vitamin and mineral supplementation.

Adverse events. The occurrence of all adverse events (AE) will be documented in all study subjects throughout the study follow-up period**.**

Quality of life questionnaires. Changes from baseline quality of life will be measured using the IWQOL and SF-36 questionnairy. The questionnaires are to be obtained at baseline and at month 1, 3, 6, 12, 24 and 36.

Table 2. The flow chart of the intervention and follow-up of the participants enroled in the study. This table depicts the schedule of interventions from baseline to follow-up.

	Baseline	Follow-up											
	< 45 days before surgery	W1	W2	W3	M1	M2	M3	M6	M12	M18	M24	M30	M36
Clinical assessment	X		X		X			X	X				
Psychological assessment	X												
Medical history	X												
Medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac safety - blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X
Anthropometry *Height (only at baseline) Weight, DXA, girth*	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening and safety labs *(blood, urine)*	X				X	X	X	X	X	X	X	X	X
Mixed meal tolerance test	X					X		X	X	X	X		
Upper GI series *(with small bowel follow-through)*	X		X										
Endoscopy						X			X				
Behavioral and dietary counseling	X				X		X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life questionnaries *(IWQOL, SF-36)*	X				X		X	X	X		X		X

W: Week; M: Month; DXA: Dual emission X-ray absorptiometry; GI: Gastro-Intestinal; IWQOL: Impact of weight on quality of life questionnaire; SF-36: 36-Item short form survey.

[Data collection]

Laboratory analysis

1) The glucose level, HbA1c, ALP, total calcium, magnesium, iron, ferritin, folate, phosphate, parathyroid hormone, total protein, albumin, AST, ALT, GGT, creatinine, vitamin A, vitamin B1, vitamin B6, vitamin B12, vitamin C and vitamin D will be determined. Analyses will be performed on Atelica Solution, Siemens, USA.
2) After completing the evaluation of these analytes, serum (plasma) aliquots will be frozen at -80° C until further analysis of other selected parameters, such as myokines (FGF21, FGF19, Spexin) and incretins (insulin, c-peptide, GLP-1, GIP, ghrelin, PYY). Serum levels of incretins will be measured on a MAGPIX instrument (Luminex Corporation, Austin, TX, USA) with the MILLIPLEX MAP human metabolic hormone panel (HMHEMAG-34K; Merck KGaA, Darmstadt, Germany). FGF21 levels (H188RB, ThermoFisher Scientific, Waltham, MA, USA), FGF19 (RD191107200R, BioVendor, Brno, Czech Republic), Spexin (MBS2533422, Baria, Psary, Czech Republic) and P1NP (MBS2021241, Exbio, Vestec, Czech Republic) will be detected in serum using ELISA.
3) One serum aliquot from baseline 6 months and 30 months after surgery will be used to measure the cytokine profile using Proteome Profiler Human Cytokine Array Kit (ARY005B; RaD Systems, Minneapolis, Canada). The following parameters will be analyzed: C5a, CD40 ligand, G-CSF, GM-CSF, CXCL1, CCL1, ICAM-1, IFNgamma, IL-1 alpha, IL-1 beta, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-16, IL-17, IL-17E, IL-18, IL-21, IL-27, IL-32 alpha, IP-10, I-TAC, MCP-1, MIF, MIP-1 alpha/beta, CCL5, SDF-1, PAI-1, TNF alpha, TREM-1. The signal will be detected using the Alliance Q9 Advanced chemilumuniscence imaging system (Uvitec Cambridge, England, UK).

Liquid chromatography-mass spectrometry detection of bile acids in plasma

Fifty microlitres of plasma will be precipitated with 160 µL of acetonitrile containing a mixture of standards (glycocholic acid-d4, taurocholic acid-d4, glycochenodeoxycholic acid-d4, cholic acid-d4 chenodeoxycholic acid-d4, and lithocholic acid-d4; all from Sigma, St. Louis, MO, USA). The resulting mixture will be vortexed and then centrifuged at 15,000×g for 10 minutes at room temperature. Subsequently, the supernatant will be dried under nitrogen at 60°C, reconstituted in 50 µL of 40% methanol and left to incubate for 1 hour at -20°C. Following another centrifugation step at 15,000×g for 10 minutes at 10°C, 10 µL of the supernatant will be subjected to analysis using liquid chromatography-mass spectrometry. Bile acid samples will be diluted 500 times with distilled water and the subsequent processing steps will be identical to those used for plasma samples. Separation of the sample will be achieved using a ternary Dionex Ultimate 3000 HPLC system (Dionex Softron GmbH, Germering, Germany) mounted with a Hypersil GOLD column (150 × 2.1 mm, particle size 3 µm; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and a SecurityGuard column (Phenomenex, Torrance, CA, USA) in a temperature-controlled column chamber. The mobile phase consisted of water, methanol, ammonium acetate (5 mmol / L) and formic acid (0.012% v/v), with a flow rate set at 0.3 mL/ min and the column chamber will be maintained at 55°C. Throughout the analysis, the concentration of the ammonium acetate will be kept at 5 mmol/L and the concentration of formic acid concentration at 0.012% (v/v). The gradient of methanol concentrations (v/v) progressed as follows: 40% from 0 to 2.5 minutes; 40 to 57% from 2.5 to 3.5 minutes; 57 to 59% from 3.5 to 9.5 minutes; 59 to 70% from 9.5 to 10.0 minutes; 70 to 72% from 10.0 to 14.0 minutes; and 72% to 76% from 14.0 to 16.0 minutes. Subsequently, the column will be washed with 95% methanol for 9 minutes and then equilibrated with 40% methanol for 5 minutes, both steps containing ammonium acetate and formic acid.

Bile acids (BA) will be detected using a TSQ Quantum Access Max triple quadrupole mass spectrometer TSQ Quantum Access Max with H-ESI II probe (Thermo Fisher Scientific, Inc., Waltham, MA, USA) operating in multiple selected reaction monitoring (SRM) mode. The monitored transitions will be as follows: for monohydroxy BA (lithocholic acid) at 375.3 → 375.3, for dihydroxy BAs (ursodeoxycholic acid, deoxycholic acid, chenodeoxycholic acid) at 391.3 → 391.3, and for trihydroxy BAs (cholic acid) at 407.3 → 407.3. Glycine-conjugated BAs will be monitored as follows: for monohydroxy at 432.3 → 432.3 (432.3 → 74.1), dihydroxy at 448.3 → 448.3 (448.3 → 74.1), and trihydroxy at 464.3 → 464.3 (464.3 → 74.1). The monohydroxy of taurine conjugated BA will be monitored at 482.3 → 482.3 (482.3 → 124.1), dihydroxy at 498.3 → 498.3 (498.3 → 124.1), and trihydroxy at 514.3 → 514.3 (514.3 → 124.1). The internal standards contained 4 deuterium atoms, increasing the m/z value by 4. All transitions will be monitored from 1 to 18 min to allow the unspecific detection of other bile acids not included in the standard mixture. The peak area of the individual metabolites will normalise to the area of the corresponding internal standard.

[Statistical analysis]

General analysis methods are described below.

Continuous outcomes - continuous outcomes will be summarised with mean, standard deviation, and other relevant statistical summaries. When not normally distributed, medians and quartiles will be reported. A confidence interval approach may be used, if appropriate, to compare outcomes with historical data. Changes in continuous variables will be assessed with pairs or unpaired t tests, as appropriate.

Binary Outcomes - binary and ordinal outcomes will be tabulated. Rates will be expressed as a percentage taking into account study subjects available for follow-up at particular time points. The confidence intervals for the proportions will be calculated using the exact binomial distribution. A confidence interval approach will be used to compare the results with historical data. Changes in proportions will be assessed using the McNemar test or Z tests, as appropriate.

Missing data - missing values will generally be ignored in analyses. Additional analyses can be performed using the 'last observation carry-forward (LOCF)' method.

Baseline information - baseline demographic and clinical variables will be summarised with standard approaches (means, standard deviations, frequency tables, etc.). Weight loss - percent total weight loss will be evaluated using a t-test versus a null hypothesis of 0 weight loss. The percentage of total weight loss will be assessed over time using repeated measures analysis of variance.

[Discussion]

Metabolic surgical procedures have traditionally been divided into three categories: restrictive, malabsorptive, or mixed surgery. This classification is made under the assumption that metabolic surgery controls only food intake and/or nutrient absorption. According to this conventional view, restrictive surgical procedures, such as LAGB or vertical banded gastroplasty (VBG), induce early satiety during meals by decreasing the volume of the stomach. Malabsorptive procedures, such as BPD, divert bile into the terminal segment of the ileum, thereby drastically reducing nutrient absorption. Mixed procedures, such as RYGB, involve restriction of the stomach and bypass of the small bowel, which is, however, shortened much less than in BPD. Other novel procedures, such as duodenojejunal bypass (DJB), ileal interposition and sleeve gastrectomy are becoming increasingly popular due to their ability to

cause dramatic weight loss and/or substantial improvement in glycemic regulation among both obese and non-obese patients.
Several gastrointestinal hormonal changes have been reported to occur after gastric surgery, consistent with the hypothesis that alterations in gastrointestinal anatomy affect the endocrine functioning of the gut. For example, RYGB induces substantial hormonal changes, even before weight loss occurs (17). Increased levels of the peptide YY and GLP-1 (18) have been consistently reported in several animal and human studies. RYGB also appears to alter ghrelin and GIP (19). All of these hormones are involved in the regulation of energy homeostasis through their effects on peripheral organs, as well as the brain. Although the exact molecular mechanisms that underlie the improvements in metabolism after gastric bypass surgery are not known, these findings establish that changes in gastrointestinal anatomy have profound effects on the control of metabolism in gastrointestinal tract (20).
Furthermore, since a number of gastrointestinal hormones and neural signals are produced at various sites in the gastrointestinal tract, different surgical methods might activate distinct mechanisms of action.
These changes in gastrointestinal hormones after different metabolic surgeries could be also associated with changes of the activity of the autonomous nervous system (21). The dominance of sympathetic activity in obese people is well known, and several authors described the weight loss benefit of autonomic control after both dietary restriction (22) and surgical interventions (23). However, metabolic surgery can also have negative effects on the cardiovascular regulation in some patients (21).
Gastrointestinal bypass and diversion procedures connect two otherwise separated segments of the gastrointestinal tract, allowing nutrients to reach the distal portion of the small intestine more rapidly than usual and bypassing the contact of nutrients with much of the stomach, the entire duodenum, and part of the jejunum. There are two major hypotheses for improvement of glycemia after gastrointestinal surgery. According to the ‘lower’ intestinal hypothesis’ (24) (also known as ‘distal’ or ‘hindgut’ hypothesis) (25), the rapid delivery of nutrients to the lower intestine increases L cell stimulation, resulting in increased secretion of hormones that enhance insulin release and/or insulin action (for example, GLP-1) and a subsequent decrease in blood glucose levels. According to the ‘upper intestinal hypothesis’ (24) (also defined as ‘proximal’ of ‘foregut’ hypothesis) (25), gastrointestinal bypass reduces the secretion of upper gastrointestinal factors that decrease insulin secretion and/or promote insulin resistance. Reduction of the amount of these putative anti-insulin factors (or anti-incretins) would increase insulin action, and therefore improve the symptoms of T2DM. Although the proximal and distal hypotheses are often conceptualised in terms of the release of hormones, they are also compatible with the theory that altered nutrient flow triggers neural signaling rather than hormone release.

[Strengths and limitations]

Strengths

One of the primary strengths of this study is the rigorous methodology employed in patient selection and data collection. The comprehensive approach ensures high-quality data and reliable findings. Additionally, the study focusses on a specific population of patients, providing detailed information on the characteristics of this group and potential treatment outcomes.

Limitations

The most significant limitation of this study probably will be the small sample size, which can affect the generalizability and statistical power of the findings. The limited number of participants reduces the ability to detect smaller effects and may lead to wider confidence intervals in the results. Consequently, the conclusions drawn from this study should be interpreted with caution, and further research with larger sample sizes will be necessary to validate these findings.

[Comparison with Prior work]

In an effort to replicate the durable results of metabolic surgery in metabolic disease while minimising its risks, Department of Obesity and metabolic syndrome, Human Motion Diagnostic Centre, University of Ostrava has developed two innovative surgical methods to perform a bowel-to-bowel anastomosis, similar to the type used in current metabolic surgeries. Methods include jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis. Side-to-side jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis provide two routes for ingested food. The new, shorter route has a malabsorptive effect similar to that seen in Roux en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) procedures which lead to weight loss. Furthermore, the delivery of nonabsorbed macronutrients to the distal ileum or transverse colon can enhance an effect of incretin and improve Type 2 Diabetes Mellitus (T2DM) parameters. However, the native route is also preserved, which theoretically reduces the risk of malnutrition, diarrhoea, and metabolic derangements seen in other metabolic surgeries. The side-to-side jejuno-ileal anastomosis was already tested in the pilot study of the GI Windows Self-Forming Magnetic (SFM) Anastomosis Device for Creation of an Incisionless Small Bowel Diversion for Treatment of Obesity and Diabetes in year 2015 (15).

[Conclusion]

Traditional metabolic surgeries are highly safe and effective in patients with severe obesity and T2DM. Furthermore, gastrointestinal diversion techniques improve glucose homeostasis through mechanisms beyond reduced caloric intake and weight loss. Continued research to better understand the weight-independent antidiabetic mechanisms of gastrointestinal surgery and the role of the gastrointestinal tract in the physiology and pathophysiology of glucose homeostasis could lead to important discoveries that can ultimately help identify targets for the development of novel drugs, as well as facilitate the design of interventions that are less invasive than current methods for the treatment of obesity and T2DM.
In summary, metabolic diseases are a growing pandemic with suboptimal clinical solutions. The surgical side-to-side jejuno-ileal anastomosis and side-to-side jejuno-colic anastomosis without gastrectomy potentially represent a new class of therapy that can produce durable clinical results generally associated with surgery while minimising its attendant risks.

[Aknowledgements]

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Ethics and dissemination

The study has been designed as a prospective nonrandomised study which conforms to the principles and guidelines of the Declaration of Helsinki, and good clinical practice and has been approved by the Ethics Committee of the Hospital Agel, Ostrava-Vítkovice, Czech Republic (no. EK/165/2019). The clinical trial registration number on Clinicaltrials.gov is NCT06374368.

Patient and public participation

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this investigation.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

[Conflicts of interests]

The authors declare no conflicts of interest.

[Abbreviations]:

AE	adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate amino transferase
BA	bile acid
BP	blood preassure
BPD	bioliopancreatic diversion
CBC	Complete blood count
DJB	duodenojejunal bypass
DPP4	dipeptidyl peptidase 4
DXA	dual-emission X-ray absorptiometry
EC	Ethics Committee
EK	Ethics Committee
EST VAT	estimated visceral adipose area
EU	European Union
GDPR	General Data Protection Regulation
GGT	Gammaglutamyltransferase)
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
HbA1c	glycated hemoglobin
HCG	Human chorionic gonadotropin

HDL	high density lipoproteins
IEC	Independent Ethics Committees (IEC)
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IWQOL	Weight on Quality of Life
JID	jejuno-ileal diversion
JCB	jejuno-colic diversion
Kg	kilogram
LAGB	laparoscopic adjustable gastric banding
LBM	lean body mass
LDL	low density lipoproteins
RYGB	Roux-en-Y gastric bypass
SF-36	Short Form Health Survey
SFM	self-Forming Magnetic
SRM	selected reaction monitoring
T2DM	type 2 diabetes mellitus
TAG	triglycerides
TSH	thyrotropic hormone
WBC	white blood cells

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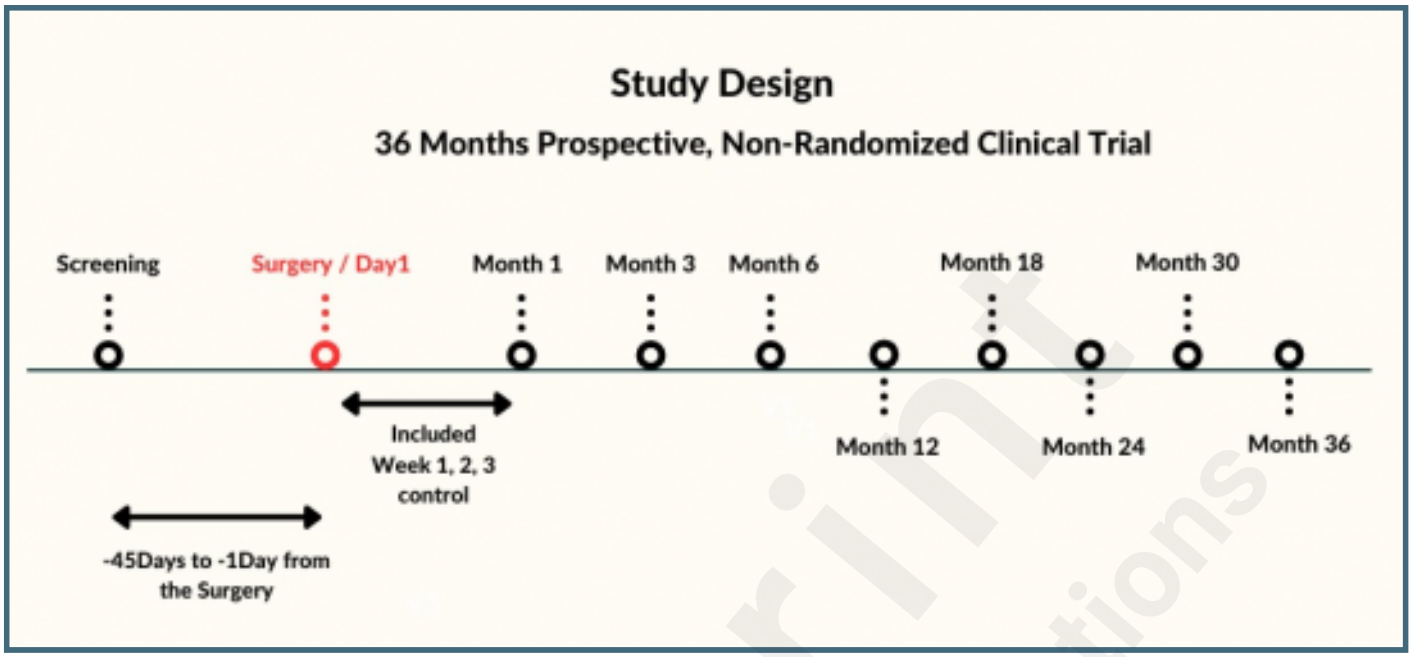
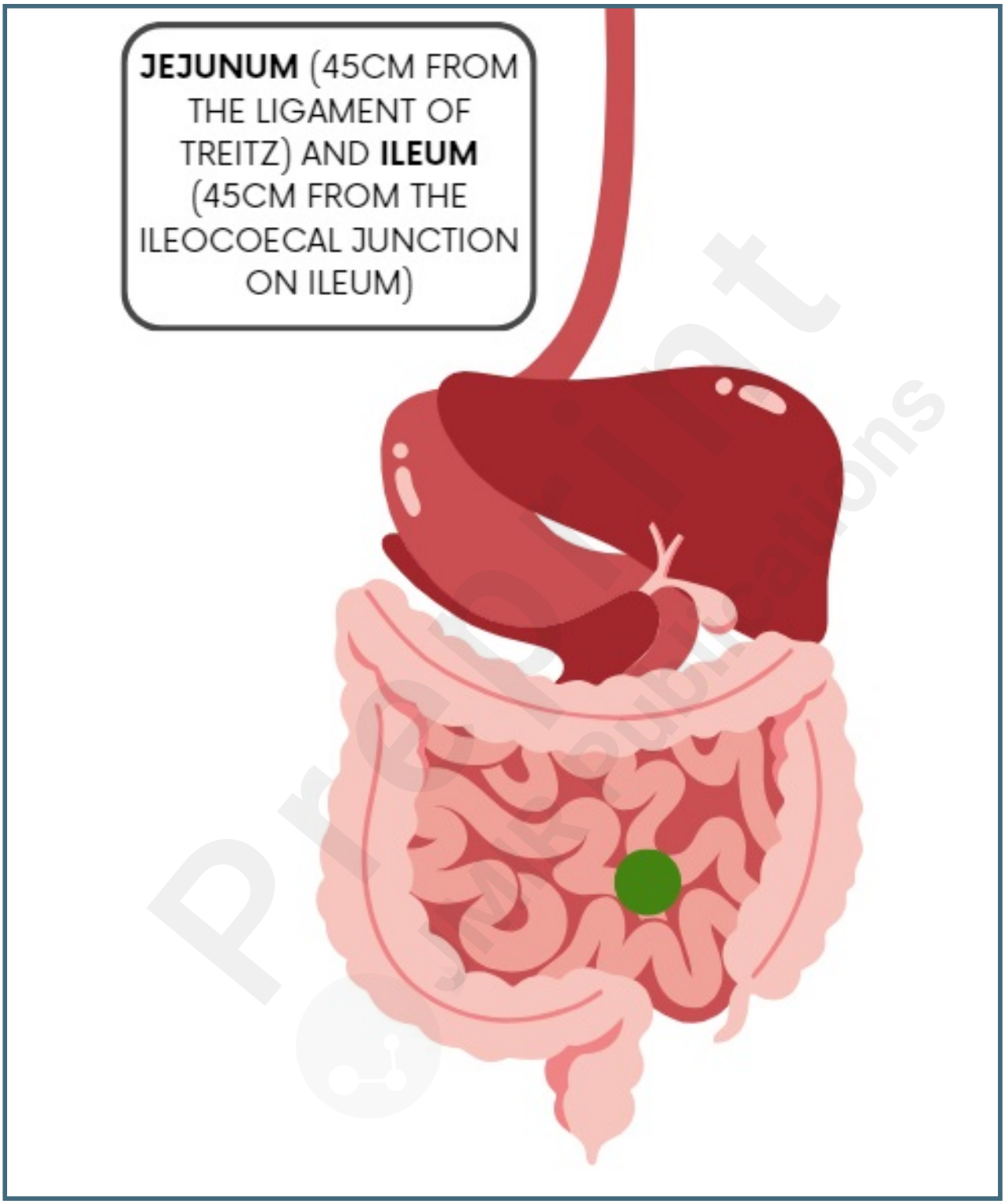
Supplementary Files

Figures

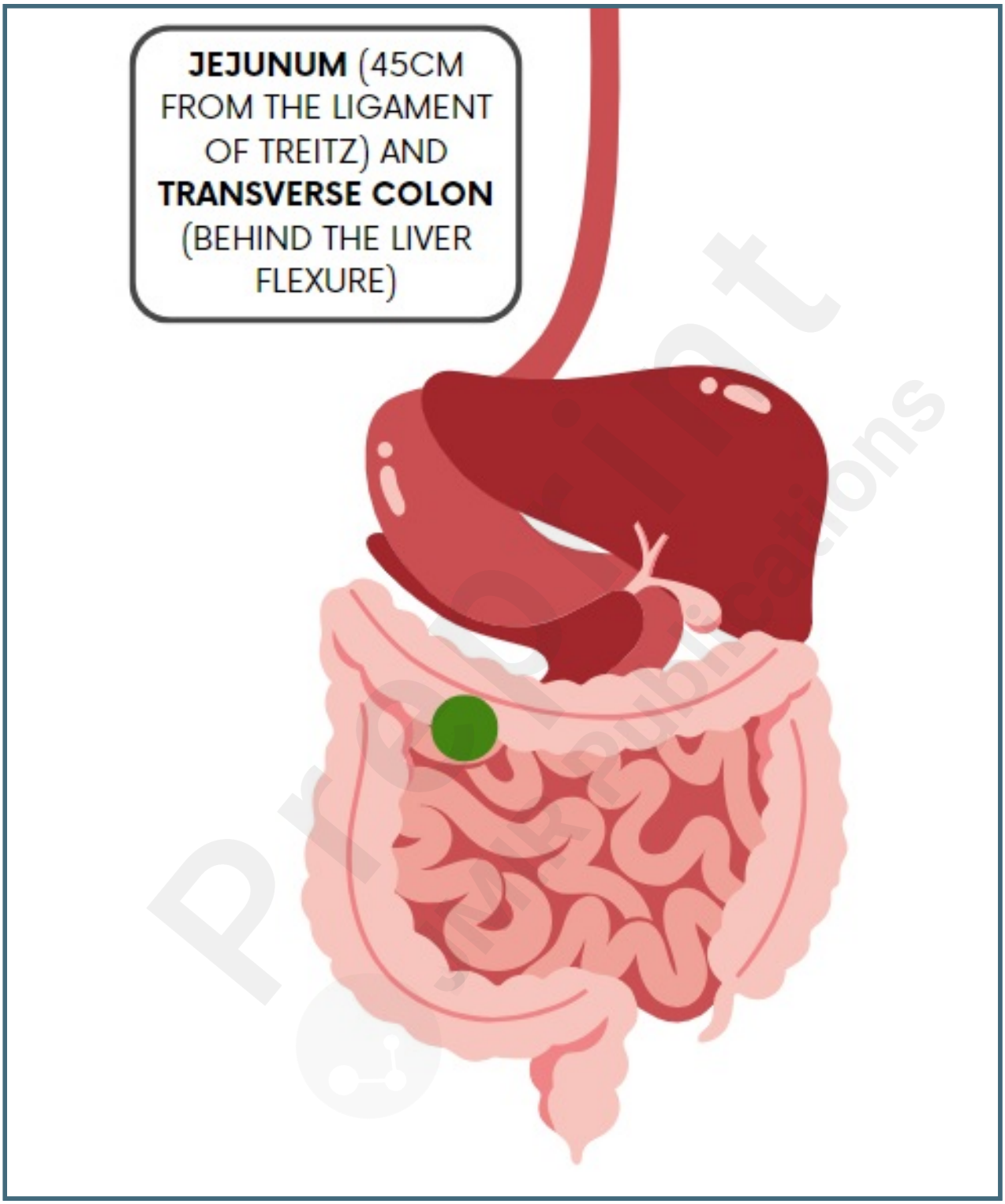
Study design - Timeline of interventions and follow-up of participants enroled in the study (created by Canva.cz).



Model of jejuno-ileal diversion (created by Canva.cz).



Model of jejuno-colic diversion (created by Canva.cz).



CONSORT (or other) checklists

Untitled.
URL: http://asset.jmir.pub/assets/e34c44588ba30dcf44863472484cc99c.pdf