Effect of Delayed-Release Bile Acid on Insulin Sensitivity, Gastric Emptying and Body Weight in Overweight or Obese Patients with type 2 Diabetes Mellitus

Version 1
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Project Summary

Background: Intra-jejunal administration of bile acids improves insulin sensitivity.

Hypothesis: The ox bile extract in delayed (ileocolonic)-release formulation, stimulates enteroendocrine L cell secretion in the ileum and colon, increasing the secretion of FGF-19, GLP-1, oxyntomodulin (OXM), and PYY_{3-36}, improving insulin sensitivity and inducing weight loss.

Aim: To study the effect of an ileocolonic formulation of ox bile extract on insulin sensitivity, postprandial plasma glycemia and incretin levels, gastric emptying and body weight in overweight or obese type 2 diabetic subjects on therapy with metformin and/or DPP-IV inhibitors.

Study design: This is a single center, placebo-controlled, parallel group, single dose randomized controlled trial to 28 days (+/- 4 days) study the effect of delayed (ileocolonic)-release ox bile extract 500 mg BID on insulin sensitivity, gastric emptying of liquids and solids (measured by scintigraphy) and weight loss in overweight or obese type 2 diabetic subjects. Participants will be receiving therapy with DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin. Blood samples will be collected at defined times to measure glycemia, FGF-19 and incretins (GLP-1, OXM, PYY_{3-36}) fasting levels and responses to the meal.

Anticipated Results: In comparison with placebo, ox bile extract will increase insulin sensitivity, enhance glycemic control, increase postprandial incretins, and delay GE of liquids.

Significance: This study will prove that ileocolonic-release ox bile extract enhances glycemic control in T2DM patients.

Background and Significance

Obesity and Type 2 Diabetes Mellitus (T2DM) are chronic illnesses whose prevalence have reached epidemic proportions in developed countries and are increasing in developing countries.[1] In the USA, the prevalence of overweight adults is 64%, and obese adults is 30.5%.[2] This alarming obesity epidemic poses a heavy burden to the U.S. economy, costing more than $150 billion every year—10 percent of the total health budget—according to the Centers for Disease Control and Prevention (CDC 2012). Patients with obesity are at a higher risk of a new-onset cardiovascular event and type 2 diabetes.[3] Nearly 24 million Americans suffer from diabetes and its associated co-morbidities. Diabetes is now the fifth leading cause of death in the US.[4] These alarming statistics reinforce the urgent need for research into the prevention of diabetes, and the prevention of the progression or complications of diabetes. Currently, the most effective treatment for obesity, metabolic syndrome and T2DM is bariatric or metabolic surgery.[5]

The efficacy in obesity and T2DM of metabolic surgery when compared to caloric restriction suggests that the mechanism on weight loss and reversal of insulin resistance and hyperglycemia exceeds the effect of diet restriction and gastrointestinal anatomical re-arrangement as in duodenal switch or Roux-en Y gastric bypass.

Recent advances on the understanding of metabolic surgery, suggest that bile acids play a role in the surgery-related improvement of diabetes. Metabolic surgery results in doubling of the concentration of serum bile acids, and increases serum adiponectin and GLP-1. Effects of bile acids in the distal small intestine results in weight loss and improved glucose homeostasis by stimulating enteroendocrine L cell secretion, and increasing FGF19, thyroid hormone - type 2 Deiodinase (D2) and decreasing endoplasmic reticulum (ER) stress.[6-9] These result in rapid increase in incretins, increased energy expenditure, decreased appetite, decreased hepatic insulin resistance and improved muscle insulin sensitivity.[10, 11]

Metabolic surgery; is invasive, has multiple side effects including perioperative complications and long term nutritional deficits.[12] Thus, metabolic surgery cannot be considered a public health remedy to the current obesity and T2DM epidemic, and a low cost, non-invasive approach that is efficacious over a long term is needed to fight this epidemic. Our overriding approach is to adopt a weight loss mechanism produced by bariatric surgery in a non-surgical remedy for treatment of obesity and T2DM. Specifically, our study will address the concept that changes in bile acid concentration in the ileum seen after metabolic surgery could be applied by non-invasive pharmacological treatment in obesity and T2DM.

Prior studies using taurocholic acid (TCA), a hydrophilic bile acid, have shown an improvement in endoplasmic reticulum (ER) stress,[13] reversal of insulin resistance and restoration of glucose homeostasis in mice with T2DM.[14] Subsequently, these results were confirmed in obese men and women showing that TCA 1,750 mg/day improves liver and muscle insulin sensitivity.[11] These results were not as dramatic as those seen after metabolic surgery. Hence, a subsequent study mimicking the role of intra-luminal bile acids after metabolic surgery was conducted by intrajejunal infusion of taurocholic acid (2 g); this resulted in acute improvement in glucose homeostasis and increased GLP-1 concentration.[10] Recently, we shown that Na-chenodeoxycholate delayed-released in the ileum and colon produces mild delay in gastric, accelerated colonic transit[15] and weight loss (preliminary data – unpublished).

The overall research goal is to study the effect of delayed-release ox bile extract on glycemic control in obesity and T2DM. The current proposal is a proof of concept, single center, placebo-controlled, parallel group, randomized control trial in patients with obesity and T2DM receiving DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin, as standard of care.

A. Specific Aims:

We hypothesize that the ox bile extract in delayed (ileocolonic)-release formulation, stimulates enteroendocrine L cell secretion in the ileum and colon, increasing the secretion of FGF-19, GLP-1, oxyntomodulin (OXM), and PYY_{3-36}, and improves insulin sensitivity and induces weight loss.

To study the effect of an ileocolonic formulation of ox bile extract on insulin sensitivity, postprandial glycemia and incretin levels, gastric emptying, body weight and fasting serum FGF-19 levels in overweight or obese type 2 diabetic subjects on therapy with DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin.

C. Preliminary data:

C.1. Obesity and T2DM research: Our research group at the Mayo Clinic has more than 30 years of experience in proof of concept randomized trials and over 300 original articles in gastrointestinal physiology and pharmacology; the lab has been funded by the NIH for the past 9 years to conduct research in obesity (DK67071).

C.2. Sodium chenodeoxycholate delayed release: We have previously demonstrated that sodium chenodeoxycholate delayed (ileocolonic)-release 1000 mg PO daily is a well-tolerated medication with minimal side effects[15, 16]. NaCDC (ileocolonic)-release 1000 mg PO daily for four days produces weight loss in healthy subjects, unpublished data (figure 1) and delays gastric emptying (figure 2) in healthy subjects (HS) and subjects with constipation predominant Irritable Bowel Syndrome (IBS-C) [15, 16]. Body weight change and gastric emptying were not end points of those studies and were incidental findings. The weight loss and gastric emptying after ONLY four days of treatment suggests that ileocolonic-release Na-CDC may be a promising method to induce weight loss in the appropriate population. Na-CDC is not available for long term clinical studies. Thus we proposed to use the FDA approved ox bile extract as a substitute.

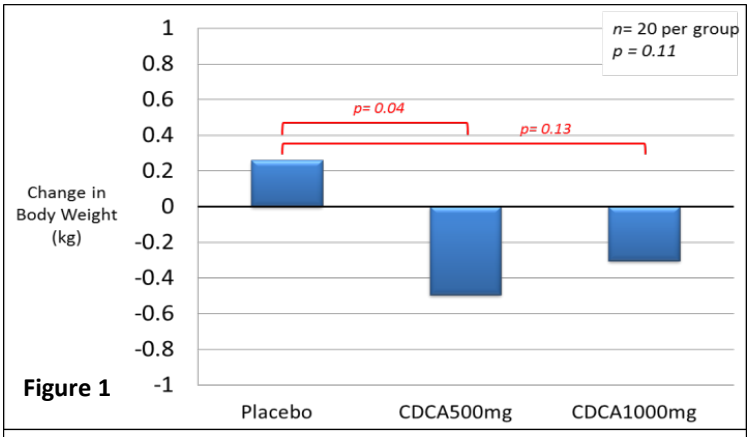


Figure 1

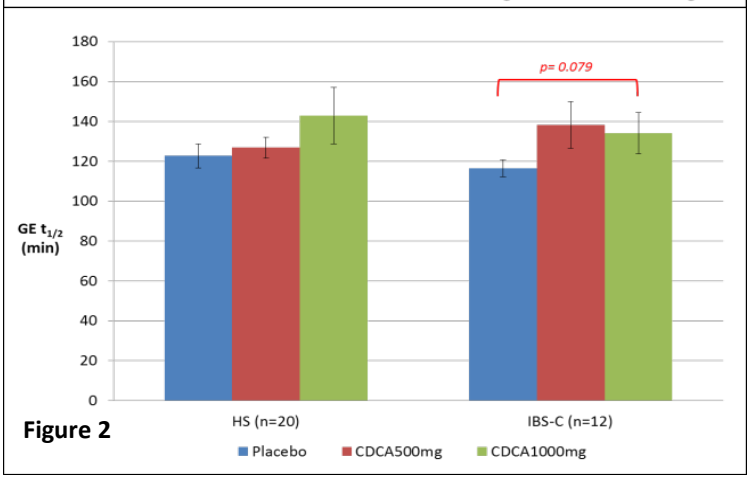


Figure 2

D. Research strategy

D.1. Rationale: Bile acid secretion increases significantly after Roux-in-Y gastric bypass and bile acids appear to have a major role in the mechanism of weight loss after metabolic surgery. Recent studies showed that intrajejunal-delivery of primary bile acids ***improve insulin sensitivity***. We ***hypothesize*** that the ox bile extract delivered through delayed (ileocolonic)-release therapy stimulates enteroendocrine L cell secretion in the distal jejunum, ileum and colon, thereby increasing the secretion of FGF-19, GLP-1, OXM, and PYY3-36. These observations suggest that bile acids may decrease blood glucose and improve insulin sensitivity through their effects on endogenous incretins, independently of gastric emptying and glucose.

D.2. Design: We propose a single center, placebo-controlled, parallel group, single dose randomized controlled 28 +/- 4 day trial to study the effect of delayed (ileocolonic)-release ox bile extract 500 mg bid on postprandial glycemia, insulin sensitivity, fasting and postprandial incretins (FGF-19, GLP-1, OXM, PYY_{3-36}), gastric emptying and weight loss in overweight or obese type 2 diabetic subjects receiving therapy with DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin.

D.3. Participants: Subjects with obesity and T2DM on therapy with DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin (standard of care) will be recruited by direct contact from an established database of patients with T2DM and BMI >30 kg/m^2 or by public advertisement. Eligible cases will be invited to participate by letter using the randomization scheme provided by the study bio-statistician. All subjects will be given a verbal explanation of the study, provided time to read and study the written consent form and its information, given opportunities to ask questions and a copy of the consent form. Participants will be informed of their right to withdraw from the study at any time without prejudice to their clinical management now or in the future. Consent will be sought by one of the medical doctor investigators or study coordinator, and consent will be documented by the participant's signature on the consent form. All recruitment or contact information will be approved by Mayo's Institutional Review Board.

The *inclusion criteria* includes:

a) *Overweight or obese subjects with BMI> 30 kg/m^2 with type 2 diabetes mellitus* taking DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin, standard of care for type 2 DM.

b) Age: 18-70 years;

c) *Gender*: men or women. Women of childbearing potential will have a negative pregnancy test before initiation of medication and within 48 hours of receiving radioisotope for the gastric emptying study.

The *exclusion criteria* includes:

a) Structural or metabolic diseases/conditions that affect the gastrointestinal system, or functional gastrointestinal disorders. For screening the bowel disease questionnaire will be used to exclude subjects with irritable bowel syndrome;
b) Subjects with stool type Bristol classification 4-7 per bowel disease questionnaire (bdq);
c) To ensure homogeneity between treatment groups we will exclude subjects with other treatment for t2dm and with HbA1c > 8% and/or fasting glucose >250 mg/dl. If an HbA1c has not been completed within 3 months of the screening visit, one will be done at the screening visit.
d) Female subjects who are pregnant or breast-feeding;
e) Concomitant use of appetite suppressants or orlistat or phentermine-topiramate ER or lorcaserin.
f) Individuals who are currently on treatment for cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, endocrine (other than t2dm) and unstable psychiatric disease;

D.4. Study Medication –24 overweight or obese type-2 diabetic adults on therapy DPP4 inhibitors (e.g. sitagliptin) alone or in combination with metformin will be randomized: 12 subjects to delayed (ileocolonic)-release ox bile extract daily and 12 subjects for matched-placebo (PO tablet twice daily) for 28 +/- 4 days. Medication will be provided by Satiogen. Subjects will take medication or placebo daily, 30 minutes prior to breakfast and evening dinner, for 28 +/- 4 days.

D5. Screening and baseline evaluations: After obtaining written informed consent, a medical history, physical exam, vital signs (pulse, blood pressure, respiration rate and temperature), height, weight, waist and hip circumference measurements, HbA1c (if not completed within 3 months) and filling out the following questionnaires, if the study participants have passed their screening evaluation, they will present themselves at the Clinical Research and Trials Unit (CRTU)in the Charlton Building on the 7th floor at Mayo Clinic in Rochester, MN.

The screening questionnaires consist of the

1) GI Screening Bowel Disease Questionnaire,
2) the Hospital Anxiety and Depression Inventory,
3) the Bristol stool scale,
4) the Physical Activity Questionnaire,
5) the Eating Patterns Questionnaire,
6) the Body Self Relations Questionnaire,
7) the Audit C Questionnaire and
8) the Weight Management Questionnaire.

We will obtain a fasting glucose level at screening.

We will also do solid and liquid gastric emptying and a mixed meal glucose tolerance test at baseline and on day 28th (+/- 4 days) after treatment. Baseline and Treatment vital signs, weight and waist and hip measurements will be taken. At day 28 (+/- 4 days), we will conduct investigation of glycemia, insulin sensitivity in response to a mixed meal. A negative urine pregnancy test is required for women of child-bearing potential 48 hours prior to radioisotope exposure in the gastric emptying tests.

See appendix A: Questionnaires

D.6. Endpoints for Analysis:

The primary endpoints for analysis will be:

a) Reduction in area above basal (AAB) for Fasting Glucose.

The secondary endpoints will be:

a) Fasting glucose;
b) Insulin sensitivity calculated by the oral minimal model;
c) Weight change, kg;
d) Insulin secretion calculated by the oral minimal model;
e) Area under the curve of GLP-1, PYY_{3-36}, OXM, and FGF-19;
f) Change in fasting Adiponectin, Leptin, DPP-IV,
g) Change in gastric emptying rates at 1, 2, and 4 hours along with gastric half-emptying times.

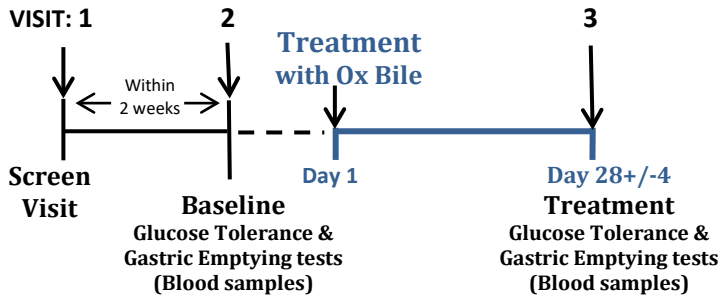
E. Materials and Methods

E.1. Delayed (ileocolonic)-release Ox Bile. After acquiring ox bile extract 500 mg tablets from Satiogen, tablets and matched placebo controls will be encapsulated in enteric coating formulated by Avomeen Analytical Services, Ann Arbor MI Subjects will take medication or matched placebo orally twice daily on an empty stomach, 30 minutes prior to breakfast and evening dinner for 28 +/- 4 days.

E.2. *Mixed Oral Glucose Tolerance Test and meal (mixed meal) gastric emptying test:* The mixed meal will be done at baseline and on day 28 (+/- 4 days) after a 10 to 12 hours fasting. Subjects will report to the Mayo Clinic CRTU Charlton 7 at the scheduled appointment time. After arrival to the CRTU, an 18 g cannula will be inserted retrogradely into a peripheral arm or hand vein. At baseline testing, participants will receive a 63g glucose in 240 ml of skim milk and a meal with 2 scrambled eggs, 50g of Canadian Bacon and one slice of bread (~560 Kcal: 43% carbohydrate, 18% protein, and 40% fat). To enable measurement of the solid and liquid phase of gastric emptying, the milk will be labeled with 0.5 mCi of ^{99m}Tc DTPA and the egg will be labeled with 0.05 mCi of In^{111}Chloride labeled activated charcoal to allow for measurement of gastric emptying and orocecal transit [22,23,24]. Scans will be acquired at the completion of the meal and every 15 minutes for the first 2 hours and then at 150, 180, 210, 240, and 360 minutes following the meal. In addition, following the mixed meal, blood samples will be collected at -30,-15, 0, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min for measurement of plasma glucose, insulin and C-peptide concentration. The results from the mixed meal will be used to calculate the area above basal (AAB) for glucose, and the oral minimal model to calculate the Insulin Sensitivity (IS) [18]. Other methods for calculating the IS will be considered [19 20]. At the conclusion of testing, the cannula will be removed and the subject will be dismissed from the CRTU.

On Day 28 (+/- 4 days), subjects will repeat gastric emptying and mixed meal testing as described above but will receive the study medication/placebo 30 minutes prior to the test meal.

E.3. Blood samples: The fasting blood samples will be collected during the mixed meal and stored -70° C freezer. We will analyze plasma glucose, insulin, C-peptide, GLP-1, PYY3-36, OXM, FGF-19, DPP-4, 7-α-C4, Adiponectin, Leptin, CCK, PP.



F. Statistical Analysis

The primary analyses will compare treatment groups at the post–4-week treatment visit using analysis of covariance (ANCOVA) models incorporating the corresponding baseline study value as a covariate (e.g., fasting or peak concentration, or AAB).

F.1.Sample size assessment - The table below summarizes data for primary response measures and uses the (relative variation, CV%) to estimate the effect size detectable with 80% power based on a two sample t-test at a two-sided α level of 0.05. The ***effect size*** is the difference in group means as a percentage of the listed mean for each response and assumes 12 subjects per group; these effect sizes are clinically significant. The ANCOVA analysis will likely provide similar power for somewhat smaller differences by incorporating relevant covariates. The data for AUC for glucose and insulin have been published[25]. Groups will be balance based on the use of gliptins and/or metformin.

Assuming n=12 per group Response Type	Mean	SD	CV%	Effect Size (%) [delta units] 80% Power	Δ/SD
AAB for Glucose (mmol/6hr)	3247	591	18%	22 (%) [703 mmol/6h]	1.2
Solid (egg meal) gastric emptying $t_{1/2}$(min)	117	34.7	30%	36 (%) [42 mins]	1.2

G. Potential Pitfalls and Precautions Taken

G.1. Potential pitfalls of minor significance in this study are: **a**) ***Selection bias*** - Participants willing to participate will likely be more motivated to lose weight. Randomization, double blind will avoid any selection

bias; b) ***Potential for type II error*** - The sample sizes have been based on appropriate statistical power for OGTT, glucose and insulin AUC endpoints for which the coefficient of variation has been thoroughly characterized in the prior literature from our lab; and c) ***Feasibility*** - We have already identified a cohort of people in our community who are type 2 Diabetics and willing to participate. We have the experience to successfully recruit 50 type 2 diabetics for the three days of testing in the CRTU.

G.2.Human Studies Aspects

G.2.a. Adverse Effects of Medications: Ox bile extract is used for gallbladder stones dissolution and prevention as a nutraceutical and food supplement. It is associated with the following potential adverse effects: nausea, diarrhea, anorexia, hypersensitivity. These are included in the consent form.

G.2.b. Radiation exposure: in this study comes from the ^{99m}Tc and ^{111}In used to measure gut transit. These exposures conform to previously approved levels of radiation exposure approved by the Radiation Control Committee at Mayo Clinic. The radiation dosimetry and organ exposures (in mrad) are minimal.

See appendix B: Dosimetry Table

G.2.c Patient risks: If the fasting glucose is greater than 250 mg/dl on either testing day, subject will be managed following standard of care in clinical setting. The recommended insulin doses will be per "Insulin sliding scale with Insulin regular: Glucose 250-259 = 3 units; 260-299 = 4 units; 300-339 = 5 units; 340-379 = 6 units; 380-399 = 7 units; >400 = call physician. Likely this subject will be excluded from the analysis.

H. Anticipated Results and Significance

We expect to demonstrate that delayed (ileocolonic)-release ox bile extract increases insulin sensitivity or reduces insulin resistance, improving glycemic control. This study will provide the basis for future pharmacological studies, exploring the effect of ox bile extract delayed (ileocolonic)-release on type 2 DM and obesity in a placebo-controlled 12 week randomized controlled trial.

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Bowel Disease Questionnaire

In the past 12 months, have you experienced the following?

QUESTION	YES	NO
1. 2 or less than 2 bowel movements/week		
2. Excessive straining or sensation of incomplete evacuation of stool on more than 25% of occasions		
3. Lumpy stools on more than 25% of occasions		
At least 3 months of continuous or recurrent symptoms of: 4. Abdominal pain or discomfort relieved by defecation		
5. Abdominal pain or discomfort associated with a change in stool frequency		
6. Abdominal pain or discomfort associated with a change in stool consistency		
7. More than 3 bowel movements per day		
8. Loose watery stools		
9. Bloating		
10. Swallowing difficulties		
11. Upper abdominal pain after meals more than once a month		
12. Abdominal bloating after meals		
13. Nausea regularly more than once a month		
14. Vomiting regularly more than once a month		
15. Heartburn regularly more than once a week		
16. Acid reflux regularly more than once a week		

Sign_____ **Date** _____

The Hospital Anxiety and Depression Questionnaire

Please read each item and **circle** the reply which best describes how you have been feeling during the past week. Don't devote too much time to your responses; your immediate reaction will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up' :

   Most of the time
   A lot of the time
   Occasionally
   Not at all

2. I still enjoy the things I used to enjoy :

   Definitely as much
   Not quite so much
   Only a little
   Hardly at all

3. I get a frightened feeling, as if something awful is about to happen :

   Very definitely and quite badly
   Yes, but not too badly
   A little, but it doesn't worry me
   Not at all

4. I can laugh and see the funny side of things :

   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all

5. Worrying thoughts go through my mind :

   A great deal of the time
   A lot of the time
   From time to time
   Only occasionally

6. I feel cheerful :

   Not at all
   Not often
   Sometimes
   Most of the time

7. I can sit at ease and feel relaxed :

   Definitely
   Usually
   Not often
   Not at all

8. I feel as if I am slowed down :

   Nearly all the time
   Very often
   Sometimes
   Not at all

9. I get a frightened feeling, like ‘butterflies in the stomach’ :

   Not at all
   Occasionally
   Quite often
   Very often

10. I have lost interest in my appearance :

    Definitely
    I don’t take as much care as I should
    I may not take quite as much care
    I take just as much care as ever

11. I feel restless as if I have to be on the move :

    Very much indeed
    Quite a lot
    Not very much
    Not at all

12. I look forward with enjoyment to things :

    As much as I ever did
    Rather less than I used to
    Definitely less than I used to
    Hardly at all

13. I get sudden feelings of panic :

    Very often indeed
    Quite often
    Not very often
    Not at all

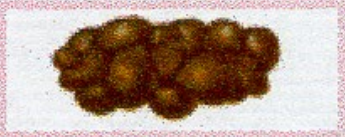
14. I can enjoy a good book or TV program :

    Often
    Sometimes
    Not often
    Very seldom

Sign_____ Date _____

Bristol Stool Scale

Circle the form which best describes your normal bowel movements.

Stool form	Appearance	Type
Separate hard lumps, like nuts (hard to pass). Result of slow transit		1
Sausage-shaped but lumpy		2
Like a sausage but with cracks on its surface		3
Like a sausage or snake – smooth and soft		4
Soft blobs with clear cut edges (easy to pass)		5
Fluffy pieces with ragged edges, a mushy stool		6
Watery, no solid pieces. Result of very fast transit		7

Ease of Passage:

1. Manual disimpaction required
2. Enema or suppository required to initiate bowel movement
3. Some straining necessary to pass bowel movement
4. Easy normal passage of stool without straining
5. Urgent need to pass bowel movement spontaneously; **no** abdominal pain or discomfort present
6. Urgent need to pass bowel movement spontaneously; abdominal pain or cramping present
7. Incontinent of bowel movements

Physical Activity Stages of Change Questionnaire

For each of the questions below, please check Yes or No. Please be sure to follow the instructions carefully.

Physical activity or exercise includes activities such as walking briskly, jogging, bicycling, swimming or any other activity where the exertion is as least as hard as these activities. Your heart rate and breathing should increase.

	NO	YES
1. I am currently **physically active**		
2. I intend to become more **physically active** in the next 6 months		

For activity to be **regular**, it must add up to a **total** of **30 minutes or more per day**, and be done **at least 5 days per week**. For example, you could take one 30 minute walk, or take three 10 minute walks each day.

	NO	YES
3. I currently engage in **regular physical activity**		
4. I have been **regularly physically active** for the past 6 months		

Sign_____ Date _____

Eating Patterns Questionnaire

1. During the past **six** months, did you often eat within any two-hour period what most people would regard as an unusually large amount of food?

__ 15

1☐ Yes 0☐ No → SKIP TO QUESTION 5

2. During the times when you ate this way, did you often feel you couldn't stop eating or control what or how much you were eating?

__ 16

1☐ Yes 0☐ No → SKIP TO QUESTION 5

3. During the past **six** months, how often, on average, did you have times when you ate this way – that is, large amounts of food **plus** the feeling that your eating was out of control (there may have been some weeks when it was not present – just average those in).

__ 17

1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ Nearly every day

4. Did you usually have any of the following experiences during these occasions?

__ 18 a. Eating much more rapidly than usual? 1☐ Yes 0☐ No

__ 19 b. Eating until you felt uncomfortably full? 1☐ Yes 0☐ No

__ 20 c. Eating large amounts of food when you didn't feel physically hungry? 1☐ Yes 0☐ No

__ 21 d. Eating alone because you were embarrassed by how much you were eating? 1☐ Yes 0☐ No

__ 22 e. Feeling disgusted with yourself, depressed, or feeling very guilty after overeating? 1☐ Yes 0☐ No

5. In general, during the past **six** months, how upset were you by overeating (*eating more than you think is best for you*)?

__ 23

1☐ Not at all
2☐ Slightly
3☐ Moderately
4☐ Greatly
5☐ Extremely

6. In general, during the past **six** months, how upset were you by the feeling that you couldn't stop eating or control what or how much you were eating?

__ 24

1☐ Not at all
2☐ Slightly
3☐ Moderately
4☐ Greatly
5☐ Extremely

7. During the past six months, how important has your weight or shape been, in how you feel about or evaluate yourself as a person – as compared to other aspects of your life, such as how you do at work as a parent, or how you get along with other people?

__ 25

1☐ Weight and shape were **not very important**
2☐ Weight and shape **played a part** in how you felt about yourself
3☐ Weight and shape **were among the main things** that affected how you felt about yourself
4☐ Weight and shape **were the most important things** that affected how you felt about yourself

8. During the past **three** months, did you ever make yourself vomit in order to avoid gaining weight after binge eating?

__ 26
__ 27

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

9. During the past **three** months, did you ever take more than twice the recommended dose of laxatives in order to avoid gaining weight after binge eating?

__ 27
__ 28

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

10. During the past three months, did you ever take more than twice the recommended dose of diuretics (water pills) in order to avoid gaining weight after binge eating?

__ 29
__ 30

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

11. During the past three months, did you ever fast – not eat anything at all for at least 24 hours --in order to avoid gaining weight after binge eating?

__ 31
__ 32

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ Nearly every day

12. During the past three months, did you ever exercise for more than an hour **specifically** in order to avoid gaining weight after binge eating?

___ 33
___ 34

1☐ Yes ——→
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

13. During the past three months, did you ever take more than twice the recommended dose of a diet pill in order to avoid gaining weight after binge eating?

___ 35
___ 36

1☐ Yes ——→
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

Sign_____ **Date** _____

Multi-dimensional Body-Self Relations Questionnaire (MBSRQ)

On a scale of 1 (very dissatisfied) to 5 (very satisfied) please indicate how satisfied you are with each of the following areas or aspects of your body:

	Very dissatisfied	Mostly dissatisfied	Neither satisfied nor dissatisfied	Mostly satisfied	Very satisfied
1. Face (facial features, complexion)	1☐	2☐	3☐	4☐	5☐
2. Hair (color, thickness, texture)	1☐	2☐	3☐	4☐	5☐
3 Lower torso (buttocks, hips, thighs, legs)	1☐	2☐	3☐	4☐	5☐
4. Mid torso (waist, stomach)	1☐	2☐	3☐	4☐	5☐
5. Upper torso (chest or breasts, shoulders, arms)	1☐	2☐	3☐	4☐	5☐
6. Muscle tone	1☐	2☐	3☐	4☐	5☐
7. Weight	1☐	2☐	3☐	4☐	5☐
8. Height	1☐	2☐	3☐	4☐	5☐
9. Overall appearance	1☐	2☐	3☐	4☐	5☐

Sign_____ **Date** _____

AUDIT-C Questionnaire

Patient Name _____ Date of Visit _____

1. How often do you have a drink containing alcohol?

- ☐ a. Never
- ☐ b. Monthly or less
- ☐ c. 2-4 times a month
- ☐ d. 2-3 times a week
- ☐ e. 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day?

- ☐ a. 1 or 2
- ☐ b. 3 or 4
- ☐ c. 5 or 6
- ☐ d. 7 to 9
- ☐ e. 10 or more

3. How often do you have six or more drinks on one occasion?

- ☐ a. Never
- ☐ b. Less than monthly
- ☐ c. Monthly
- ☐ d. Weekly
- ☐ e. Daily or almost daily

AUDIT-C is available for use in the public domain.

MAYO CLINIC

Weight Management Questionnaire

TO BE SCANNED
QUESTIONNAIRE

Instructions: It is very important that you fill out this questionnaire **completely**. A complete questionnaire helps your nutrition team provide the best care for you. **Return the completed form to your registered dietitian (RD) or Endocrinology provider at the time of your appointment.**

Patient Information

Mayo Clinic Number	Patient Name *(First, Middle, Last)*	Date Today *(Month DD, YYYY)*

Living Situation

☐ Alone ☐ With others, describe_____

Employment

☐ Full-time ☐ Part-time ☐ Disabled ☐ Retired ☐ Unemployed ☐ Homemaker

Weight History

How old were you when you first became overweight?

☐ 10-20 years old ☐ 20-30 years old ☐ 30-40 years old ☐ 40-60 years old ☐ greater than 60 years old

What is the most you have ever weighed?

_____pounds How old were you?_____

Can you identify significant life events when you gained weight (i.e., pregnancy, menopause, new job, etc.)?

☐ No

☐ Yes

If yes, what events? _____

What is the least you have weighed since 18 years of age?

_____pounds How old were you?_____

How long did you maintain that weight? _____months or _____years

What did you weigh (if not applicable, leave blank):

Graduating high school _____ pounds

On union/wedding day _____ pounds Age_____years old

One year ago _____ pounds

Three months ago _____ pounds

Today _____ pounds

Weight-Related Complications

Indicate which of the following weight-related conditions you are experiencing.

☐ Diabetes or elevated blood glucose

☐ Heartburn/reflux (GERD)/indigestion

☐ High blood pressure (hypertension)

☐ High cholesterol (hyperlipidemia)/Coronary artery disease (CAD)

☐ Obstructive sleep apnea (OSA) or difficulty sleeping

☐ Joint pain

☐ Asthma

☐ Other, specify _____

Family

Instructions: Indicate members of your family who are or have been overweight and whether they have experienced any of the problems listed below.

	Overweight						
	Less than 20 pounds	20 to 50 pounds	More than 50 pounds	High Blood Pressure	Diabetes or High Blood Glucose	High Cholesterol	Heart Disease
Mother	☐	☐	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐	☐	☐
Brother(s)	☐	☐	☐	☐	☐	☐	☐
Sister(s)	☐	☐	☐	☐	☐	☐	☐

Past and Current Weight Control Measures

Instructions: Complete the table below about various methods you have used to control your weight.

	Previously?		Currently?			
Methods used to control weight	**Yes**	**No**	**Yes**	**No**	**Pounds Lost**	**Pounds Regained**
Dieting on your own? If yes, briefly explain.	☐	☐	☐	☐		
"Commercial" weight loss plan/system (i.e.,Weight Watchers, Overeaters Anonymous, Atkins, other, etc.) If yes, briefly explain.	☐	☐	☐	☐		
Surgeries (weight loss). If yes, specify **date** and **type** of surgery.	☐	☐	☐	☐		
Have you ever used or engaged in the following to control your weight:						
Caffeine, "energy" drinks or pills	☐	☐	☐	☐		
"Water" pills	☐	☐	☐	☐		
Vomiting	☐	☐	☐	☐		
Laxatives	☐	☐	☐	☐		
Prolonged fasting (greater than 24 hours)	☐	☐	☐	☐		
Other_____	☐	☐	☐	☐		
Have you ever been **prescribed** medication to help control your weight (i.e., orlistat [Alli, Xenical], sibutramine [Meridia], phentermine, other)? If yes, briefly explain.	☐	☐	☐	☐		

Nutritional Supplements

Do you take nutritional supplements?

☐ No
☐ Yes If yes, describe below.

☐ Multi-vitamin/mineral

☐ Calcium
_____milligrams (mg) _____times/day

☐ Vitamin D
_____international units (IU) _____times/day

☐ Calcium plus vitamin D (combined supplement)
_____milligrams (mg) of calcium _____ international units (IU) of vitamin D _____times/day

☐ Other (herbs, extracts, protein powder/bars, fish oil) _____
_____

Physical Activity

Do you regularly exercise (i.e., go for walks, go jogging, go to a health club, go swimming)?

☐ No
☐ Yes If yes, briefly describe what you do for exercise, how often, and for how long. _____
_____

Do you often stay active doing other things (i.e., your job, yard work, farming, etc.)?

☐ No
☐ Yes If yes, briefly describe what you do, how often, and for how long. _____
_____

What do you feel are the primary factors limiting you from doing more physical activity (check all that apply)?

☐ Pain (joint, nerve) during or after physical activity
☐ Do not enjoy physical activity/boring
☐ Do not have enough time
☐ Self-conscious while being physically active
☐ Too tired/fatigued
☐ Not sure what type of activity to do
☐ Not sure how to safely be active
☐ Other. Briefly describe. _____
_____

Eating Patterns and Preparation

Have you ever talked with a registered dietitian (RD)?

☐ No
☐ Yes If yes, when and for what reason? _____
_____

How many meals do you usually eat each day?

On work days _____ On days off_____

Do you snack (eat between main meals)?

☐ No
☐ Yes How often? _____times/day
What time of day?_____
What do you usually snack on? _____
_____

Who prepares most of the food you eat?

☐ You ☐ Spouse ☐ Family Member ☐ Other, describe _____

Do you eat out at restaurants?

☐ No
☐ Yes Breakfast_____times/week Lunch_____times/week Dinner_____times/week

Eating Patterns and Preparation

Do you ever feel your eating is out of control or that you eat an excessive amount of food at one time?

☐ No
☐ Yes If yes, describe how often this occurs and what types of situations result in this behavior?_____
_____

Do you feel something other than what you eat and drink explains your difficulty controlling your weight (i.e., slow metabolism)?

☐ No
☐ Yes If yes, explain_____
_____

List the types and amounts of foods and beverages you usually eat for each of the meals/snacks listed below.

Breakfast: ☐ Yes ☐ No	**Morning Snack:** ☐ Yes ☐ No
Lunch: ☐ Yes ☐ No	**Afternoon Snack:** ☐ Yes ☐ No
Evening Meal: ☐ Yes ☐ No	**Evening Snack:** ☐ Yes ☐ No

Fill in the blanks below. About how often do you consume the various foods and beverages listed during a usual week?

Sugar, Honey, Jelly/Jam, Syrup _____ times per week Butter, Margarine, Added Oil _____ times per week Cake, Pie, Ice Cream, Candy _____ times per week	Milk *(8 ounces)* (Check one) ☐ Whole ☐ 2% ☐ 1% ☐ Skim _____ times per week Yogurt *(6-8 ounces)* _____ times per week Cheese, types_____ _____ times per week
Beef, Chicken, Pork, Lamb, Veal *(4 ounces, about the size of a deck of cards)* _____ times per week Fish *(4 ounces, about the size of a deck of cards)* _____ times per week	Vegetables *(½ cup serving)* _____ times per week
Fruit *(1 serving)* _____ times per week Fruit Juices *(6-8 ounces)* _____ times per week	Beer, Wine, Liquor *(1 serving)* _____ times per week Carbonated Beverages/Soft Drinks ☐ Diet ☐ Regular _____ times per week
Breads _____ times per week Other Starches (rice, noodles, potatoes) _____ times per week	

Food Guide

Grains	Vegetables	Fruits	Milk	Meat and Beans
6 oz. per day	2 ½ cups per day	2 cups per day	3 Cups per day	5 ½ oz. per day

Appendix B: Dosimetry per administration

Model:
Adult

RAM	Activity per administration (mCi)	Activity per administration (MBq)	Number of administrations	Organ/Wt (organ doses are in mCy) Testes 0.1	Ovaries 0.1	Breast 0.05	RBM 0.12	Lung 0.12	Thyroid 0.05	Bone 0.01	Colon 0.12	Stomach 0.12	Bladder 0.05	Liver 0.05	Esoph 0.05	Other: SI 0.025	Remainder 0.025
Tc-99m Non-Absorbable Markers (solids, oral)	0.5	18.5	1	0.02	0.48	0.01	0.09	0.02	0.00	0.09	1.85	1.09	0.13	0.08	0.01	1.13	0.07
In-111 Non-Absorbable Markers (liquid, oral)	0.05	1.85	1	0.06	0.78	0.01	0.18	0.01	0.00	0.06	2.83	0.22	0.22	0.06		0.93	0.07
Total				0	1	0	0	0	0	0	5	1	0	0	0	2	0

	Remainder organ	adrenal	brain	kidney	muscle	pancreas	SI	spleen	thymus	uterus	Weighted Average
	Mass (g)	14	1420	310	28000	100	640	180	20	80	
Tc-99m Non-Absorbable Markers (solids, oral)	Organ dose	0.07	0.00	0.12	0.07	0.20		0.14	0.01	0.30	0.07
In-111 Non-Absorbable Markers (liquid, oral)	Organ dose	0.04		0.08	0.08	0.08		0.06		0.31	0.07

E (mSv): **0.97**

Additional Comments:
Ref. - <insert reference>
In-111 non absorb. markers (liquid): Ref. ICRP 53, pg. 250.

Tc-99m non absorb. Markers (solids): Ref. ICRP 80, table 3.13.2.

Remainder are mass weighted average of named remainder organs (ICRP 60).

Sample Bowel Diary: Predose to Day 5:

Effect of Delayed-Release Bile Acid on Insulin Sensitivity, Gastric Emptying and Body Weight in Overweight or Obese Patients with Type 2 Diabetes Mellitus

IRB # 15-007765

Bowel Habit Diary

Predose and through Day 5
Of study medication/placebo

Dates:_____ to _____

Andres Acosta Cardenas, MD,
Principal Investigator

Sara Linker Nord, LPN
Pager: 507- 538-2479
Phone: 507-266-1999

Daily Diary

Date_____

☐ No Bowel Movements today.

Study #_____

	Describe the consistency of bowel movement	Describe the Ease of Passage of bowel movement	Did you feel like you completely emptied your bowels?
	1 hard lumps **2** lumpy sausage **3** cracked sausage **4** smooth sausage **5** soft lumps **6** Mushy **7** watery	**1** Manual Disimpaction **2** Enema needed **3** Straining needed **4** Normal **5** Urgent w/o pain **6** Urgent w/pain **7** Incontinent	**1** no **2** yes
1 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
2 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
3 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
4 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
5 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
6 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
7 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐

Have you had any unusual negative events today? **No** ☐ **Yes** ☐ *(complete below)*

Event _____ Mild / Moderate / Severe Resolved / Ongoing

Event _____ Mild / Moderate / Severe Resolved / Ongoing

Have you taken any medications other than those you routinely use today? **No** ☐ **Yes** ☐ *(complete below)*

Medication _____	**Medication** _____	**Medication** _____
Dose _____	**Dose** _____	**Dose** _____
Time _____	**Time** _____	**Time** _____

Sample Postdose Diary:

Effect of Delayed-Release Bile Acid on Insulin Sensitivity, Gastric Emptying and Body Weight in Overweight or Obese Patients with Type 2 Diabetes Mellitus

IRB # 15-007765

Bowel Habit Diary

Final 5 Days
Of study medication/placebo

Dates:_____ to _____

Andres Acosta Cardenas, MD,
Principal Investigator

Sara Linker Nord, LPN
Pager: 507- 538-2479
Phone: 507-266-1999

Daily Diary

Date_____

☐ No Bowel Movements today.

Study #_____

Dose 1: ____:____AM **Dose 2:** ____:____PM

Take one (1) Tablet twice a day: 30 minutes before Breakfast and 30 minutes before Dinner.

	Describe the consistency of bowel movement **1** hard lumps **2** lumpy sausage **3** cracked sausage **4** smooth sausage **5** soft lumps **6** Mushy **7** watery	**Describe the Ease of Passage of bowel movement** **1** Manual Disimpaction **2** Enema needed **3** Straining needed **4** Normal **5** Urgent w o/pain **6** Urgent w /pain **7** Incontinent	**Did you feel like you completely emptied your bowels?** **1** no **2** yes
1 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
2 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
3 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
4 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
5 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
6 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐
7 ☐☐ hr. ☐☐ min ☐ am ☐ pm	☐	☐	☐

Have you had any unusual negative events today? **No** ☐ **Yes** ☐ *(complete below)*

Event _____ Mild / Moderate / Severe Resolved / Ongoing

Event _____ Mild / Moderate / Severe Resolved / Ongoing

Have you taken any medications other than those you routinely use today? **No** ☐ **Yes** ☐ *(complete below)*

Medication _____	**Medication** _____	**Medication** _____
Dose _____	**Dose** _____	**Dose** _____
Time _____	**Time** _____	**Time** _____