PROTOCOL

REMIT SITA Trial

An open-label, randomized, parallel design trial to compare the efficacy of a sitagliptin-based metabolic intervention versus standard diabetes therapy in inducing remission of type 2 diabetes.

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1.0 Hypothesis

In patients with recently-diagnosed T2DM, a 12-week course of sitagliptin, metformin, basal insulin glargine and lifestyle approaches will achieve drug-free diabetes remission in a higher proportion of patients than standard diabetes therapy at 24 weeks (3 months after the drugs are stopped).

2.0 Objectives

2.1 Primary: To determine whether the 12-week metabolic intervention with sitagliptin is more effective in achieving drug-free remission of type 2 diabetes than standard diabetes therapy when evaluated at 24 weeks after randomization.

2.2 Secondary: To determine whether the 12-week metabolic intervention with sitagliptin is more effective in achieving drug-free diabetes remission than standard diabetes therapy when evaluated at 36 weeks and at 64 weeks

2.3 Safety: To determine the rates of severe hypoglycemic episodes in the two treatment groups during 64 weeks of follow-up

3.0 Background and Rationale

The current approach to treating type 2 diabetes mellitus (T2DM) is to add progressively higher doses and numbers of glucose-lowering drugs to lifestyle approaches. People with type 2 diabetes are therefore taking such drugs from shortly after diagnosis until the end of their lives. A different, novel approach that intensively treats patients with several agents and lifestyle approaches for up to 2-4 months, followed by cessation of all drugs, may achieve a drug-free metabolic remission that could last for months to years. Such an approach has not been formally tested. However, a) evidence from small studies[1-7] suggesting that approximately 40% of newly diagnosed patients can achieve a remission with short-term intensive treatment with insulin; b) a growing list of glucose-lowering drugs with novel mechanisms of action; and c) the appeal of remission-induction versus lifelong chronic therapy highlight the need to characterize strategies for metabolic remission of diabetes and to identify the optimal therapies and regimens for achieving remission.

We recently finished a peer-reviewed pilot trial of this approach in one centre. People with T2DM diagnosed within the prior 3 years were randomized to 3 treatment groups: a) 8-week intensive metabolic intervention; b) 16-week intensive metabolic intervention; and c) standard

diabetes therapy. The intensive metabolic intervention combined lifestyle therapy with basal insulin glargine, metformin and acarbose and aimed at achieving normoglycemia on therapy. The trial (funded by the Canadian Diabetes Association, Population Health Research Institute and local donations) randomized 83 people. The mean (standard deviation) fasting and 2-hour capillary glucose levels while on the metabolic intervention were: a) 5.2 (0.5) and 6.2 (0.8) mmol/L respectively at 8 weeks; and 4.9 (0.5) and 6.0 (0.7) mmol/L respectively at 16 weeks. As follow-up is ongoing, the data cannot yet be analyzed by treatment group. However when the treatment and control groups were analyzed together, 28 of 80 participants (35%) who reached 21 weeks of follow-up achieved a diabetes remission defined as a fasting plasma glucose <7.0 mmol/L and a 2-hour plasma glucose <11.1 mmol/L on an oral glucose tolerance test (OGTT) conducted 4-12 weeks after stopping glucose-lowering medications. These short-term data illustrate that metabolic interventions such as the one proposed herein can be successfully implemented and have the potential to induce a diabetes remission not requiring glucose-lowering therapies.

The current multicentre randomized controlled trial will assess the remission-related efficacy of an incretin-based regimen in a broader set of patients. It builds on the pilot trial and other trials to identify a menu of metabolic remission strategies that can then be refined and tailored to individual needs based on future research. Such an approach represents a fresh innovative approach that could turn the therapy of type 2 diabetes from a lifelong burden of drugs to either one-time or intermittent remission-induction courses that may translate into better overall quality of life and health-related outcomes.

4.0 Design and Participants

This is a multicentre, open-label, randomized controlled trial in 100 patients with early T2DM. The trial will have the following inclusion and exclusion criteria:

4.1 Inclusion criteria

a) men and women 30-80 years of age inclusive;
b) type 2 diabetes mellitus diagnosed by a physician within 5 years prior to patient enrollment;
c) anti-diabetic drug regimen (either drug or dose of drug) unchanged during 8 weeks prior to screening and randomization;
d) HbA1C $\leq$ 9.5% on no hypoglycemic agents or HbA1C $\leq$ 8.0% on 1 agent or on half-maximal doses of 2 agents;
e) body mass index $\geq$ 23 kg/m^2;
f) a negative pregnancy test and an agreement to use a reliable method of birth control for the duration of the trial in all females with childbearing potential;
g) ability and willingness to perform self-monitoring of capillary blood glucose (SMBG); ability and willingness to self-inject insulin;
h) provision of informed consent.

4.2 Exclusion criteria

a) current use of insulin;
b) history of hypoglycemia unawareness; history of severe hypoglycemia requiring assistance within the last 5 years;
c) renal dysfunction as evidenced by serum creatinine (Cr) ≥ 124 μmol/l;
d) history of lactic acidosis or diabetic ketoacidosis;
e) active liver disease or elevated alanine transferase (ALT) levels ≥ 2.5 times upper limit of normal at the time of enrollment;
f) history of pancreatitis;
g) cardiovascular disease including any of: a) systolic blood pressure > 180 mmHg or diastolic blood pressure > 105 mmHg; b) peripheral vascular disease; c) left bundle branch block or second or third degree AV block; d) tachyarrhythmias or bradyarrhythmias with uncontrolled ventricular rate; e) stenotic valvular heart disease; f) cardiomyopathy; g) history of heart failure; h) history of aortic dissection; i) documented history of angina or coronary artery disease; j) history of stroke or transient ischemic attack;
h) history of any disease requiring continuous systemic glucocorticoid treatment;
i) history of any major illness with a life expectancy of < 3 years;
j) history of injury or any other condition that significantly limits participant's ability to achieve moderate levels of physical activity;
k) excessive alcohol consumption (>14 alcoholic drinks per week in men and >7 alcoholic drinks per week in women);
l) known hypersensitivity to insulin glargine, metformin, or any DPP-4 inhibitor.

Participants will be randomized to 2 treatment groups: (a) a 12-week course of treatment with sitagliptin, metformin, insulin glargine and lifestyle therapy, and (b) standard diabetes therapy, and followed for a total of 64 weeks (1 year and 3 months). In all participants with HbA1C<7.3%, glucose-lowering medications will be discontinued at 12 weeks, and participants will be encouraged to continue with lifestyle modifications and regular glucose monitoring. Participants who meet criteria for hyperglycemia relapse will receive standard glycemic management as informed by the 2013 Canadian Diabetes Association clinical practice guidelines[8]. Participants found to have HbA1C ≥7.3% during week 12 of the trial will also receive standard glycemic care.

The primary outcome in this trial will be diabetes remission evaluated at 24 weeks. Diabetes remission is defined as a HbA1C<6.5% off glucose-lowering agents for at least 12 weeks (3 months). The primary safety outcome will be the rate of severe hypoglycemic episodes in the treatment groups during 64 weeks of follow-up. Key secondary outcomes will be diabetes remission at 36 and 64 weeks (6 and 12 months after stopping glucose-lowering medications).

5.0 Procedures

5.1 Screening and Randomization

After obtaining informed consent at the screening visit, eligibility criteria will be assessed by performing an interview, physical examination, laboratory tests and electrocardiogram (ECG) at a local research centre. Blood will be drawn for creatinine, ALT, FPG, and HbA1C. A urine pregnancy test will be performed in women with childbearing potential. A baseline

electrocardiogram (ECG) will be also performed to assess for any evidence of ischemic heart disease or arrhythmia. Fasting blood samples will be collected for storage in participants who consent to it (see Section 5.5 and Table 1 for details). Eligible participants will be randomized to (i) 12-week intensive treatment with lifestyle, insulin glargine, metformin and sitagliptin and (ii) standard diabetes therapy. A randomization schedule will be prepared by an independent statistician using a computer-generated random number sequence and it will be stratified by centre. Study group allocation will be carried out through an online central system.

5.2. Interventions

Participants will be randomly allocated to either a sitagliptin-based metabolic intervention (comprising an induction phase followed by a maintenance phase), or standard diabetes care.

5.2.1 Sitagliptin-based Metabolic Intervention Group: Induction Phase

A 12-week metabolic intervention will be used in intervention group participants for induction of a normoglycemic state. The intervention will include treatment with basal insulin glargine, metformin, lifestyle changes and sitagliptin. The overall goals of the lifestyle intervention are to achieve and maintain ≥ 150 min of moderate physical activity per week by week 12 and ≥ 5% reduction in baseline weight by week 36 of the trial. At baseline, intervention group participants will meet with research staff who will prescribe a personalized low-calorie low-fat diet and a moderate-intensity exercise program based on current physical activity patterns and medical history. Lifestyle goals will be reinforced at each study visit. Glucose-lowering agents will be titrated gradually to minimize side effects. Sitagliptin/metformin will be started at a dose of 50/500 mg po (orally) once daily (OD) for 4 days, then increased to 50/500 mg twice daily (bid) for 4 days, then 50/850 mg bid for 4 days, then 50/1,000 mg po bid. Participants will be concurrently started on insulin glargine 2 units sc at bedtime, and the dose will be titrated by the participant with guidance from the research team aiming to achieve a fasting glucose of 4.0-5.3 mmol/l on self-monitoring of capillary blood glucose (SMBG). The overall goal will be to finish medication titration by the end of week 2, and to maintain the fasting glycemic target of 4.0-5.3 mmol/l for the remaining duration of the metabolic intervention. All other glucose-lowering medications will be discontinued.

At the first study visit, participants will be taught how to self-monitor capillary blood glucose, how to recognize and treat hypoglycemia, and how to administer and titrate study medications. Participants will be asked to monitor glucose at least twice daily before meals and during exercise.

5.2.2 Sitagliptin-based Metabolic Intervention Group: Maintenance Phase with Lifestyle Therapy

Oral glucose-lowering agents will be discontinued after 12 weeks and insulin tapered over a 5-day period in participants with HbA1C<7.3%. Participants will be encouraged to continue with lifestyle modifications. Participants will be asked to monitor fasting glucose at least 3 times per week and call research staff if they have fasting levels >10 mmol/L. Participants who have fasting glucose levels >10 mmol/L on ≥50% of SMBG readings over 1 week in the absence of an acute illness will be considered to have hyperglycemia relapse. Otherwise, *hyperglycemia relapse will be defined as (a) a fasting plasma glucose ≥ 7.0 mmol/L or a 2-hour pc plasma glucose (PG) ≥ 11.1 mmol/L on the OGTT, or (b) HbA1C ≥ 6.5%.* Participants meeting criteria

for hyperglycemia relapse and all intervention group participants at 64 weeks will return to standard glycemic care, which will be provided by participants' regular physician.

5.2.3 Control group

At the beginning of the trial, a research nurse will meet with standard group participants to review self-monitoring of blood glucose, management of hypoglycemia, and the importance of healthy diet and regular exercise in diabetes management. Glucose levels in standard group participants will be managed by their regular health care provider according to the 2013 CDA clinical practice guidelines. Any approved glucose-lowering medications will be allowed in the control group, including biguanides, DPP-4 inhibitors, GLP-1 receptor agonists and insulin. In control group participants with HbA1C<7.3%, glucose-lowering agents will be discontinued after 12 weeks and insulin will be tapered over a 5-day period. Participants will be asked to monitor fasting glucose at least 3 times per week and call research staff if they have fasting levels >10 mmol/L. Participants meeting criteria for hyperglycemic relapse (see section 5.2.2 for definitions) and all participants at 64 weeks will return to standard glycemic care.

5.3 Monitoring

Research staff will meet with intervention group participants every 1-2 weeks during week 1-12 of the trial and will contact them by telephone at least once a week between visits to review glucose readings, medication titration, medication adherence and side effects (see visit schedule). Participants will then be contacted once a month to review glucose readings and screen for symptoms of hyperglycemia. Control group participants will be contacted every 1-1.5 months during the trial to review glucose readings, medication adherence and side effects. Symptomatic and severe hypoglycemic episodes will be documented and reviewed with the treating physician promptly. *Symptomatic hypoglycemic episode* will be defined as an event with clinical symptoms consistent with hypoglycemia. *Severe hypoglycemic episode* will be defined as an event with clinical symptoms consistent with hypoglycemia requiring the assistance of another person to treat which is accompanied by either (i) a self-measured or laboratory glucose level of ≤ 2.0 mmol/L or (ii) a prompt recovery following treatment with carbohydrates or glucagon. All participants will be asked to come back for a final clinic visit at 64 weeks after randomization.

5.4 Duration of Follow-up

In order to complete recruitment in 12 months, participants will be recruited at 5 Canadian sites. Total trial duration is estimated to be 2.5 years based on a 3-month start-up period, 12-month recruitment period and 15-month follow-up period.

5.5 Measurements and Study Outcomes

HbA1C will be measured locally at baseline and 12, 24, 36, 48 and 64 weeks after randomization by a National Glycohemoglobin Standardization Program certified method. Fasting plasma glucose will be performed at baseline and at 16 weeks. Standard 75 g OGTT will be performed at 24 weeks after randomization and participants on glucose-lowering medications will be asked to hold them for 48 hours prior to the test unless fasting capillary glucose rises above 12 mmol/l. The OGTT will be performed in the morning, after overnight fasting. Blood samples for glucose will be drawn at 0 minutes and 120 minutes after administration of the 75 g oral glucose load. Fasting blood samples will be collected for storage at baseline and at 16 weeks in participants who consent to it. Genetic markers and analytes related to diabetes remission and/or diabetes complications will be measured in the stored samples. Participants will be asked to hold

glucose-lowering medications for 48 hours prior to these tests unless fasting capillary glucose rises above 12 mmol/l. Physical activity and food frequency questionnaires will be administered at baseline and at 12, 24, 36, 48 and 64 weeks. A quality of life questionnaire will also be administered at baseline, 12 and 64 weeks.

5.5.1 Primary Outcomes

a) The primary outcome in this trial is diabetes remission evaluated at 24 weeks after randomization. Diabetes remission is defined as a HbA1C<6.5% off glucose-lowering agents for at least 12 weeks (3 months).
b) The primary safety outcome will be the rate of severe hypoglycemic episodes during 64 weeks of follow-up.

5.5.2 Secondary Outcomes

a) Diabetes remission off glucose-lowering therapy at 36 and 64 weeks after randomization.
b) Drug-free normal glucose tolerance (NGT) at 24 weeks after randomization. NGT is defined as a FPG < 6.1 mmol/l and a 2-hour PG < 7.8 mmol/l on a 75 g OGTT.
c) Duration of diabetes remission in weeks.
d) The change in weight, BMI, waist circumference and waist to hip ratio from baseline to 12, 24, 36 and 64 weeks after randomization.

6.0 Statistical Analyses

A detailed statistical analysis plan will be prepared by investigators and analyses will be performed by a trained statistician at the Population Health Research Institute.

All group comparisons will be conducted according to the intention-to-treat principle with inclusion of data from all participants according to their treatment group assignment, regardless of adherence to therapy. The primary outcome in this study is diabetes remission off therapy 24 weeks after randomization. Proportion of participants in remission will be compared between the intervention group and the control group using a one-sided chi-squared test with $\alpha = 0.05$ level of significance. The outcome will be reported as a risk difference in the induction of diabetes remission between the intervention group and the control group with 95% confidence intervals. For secondary analyses, a chi-squared test will be used for dichotomous outcomes and a two-sample t-test (or a non-parametric equivalent) for continuous outcomes. Clinical and metabolic predictors of the successful induction of diabetes remission at 24, 36 and 64 weeks after randomization will be evaluated using logistic regression modeling. We will evaluate whether age, gender, ethnicity, diabetes duration, smoking, family history of diabetes, baseline BMI, waist circumference, HbA1C or fasting plasma glucose predict those participants who maintain diabetes remission at 24, 36 and 64 weeks after randomization.

7.0 Sample Size Considerations

The sample size calculation is based on the estimated proportion of patients achieving diabetes remission of $p = 0.10$ in the control group. The control group estimate of 10% is based on the proportion of patients in the conventional diabetes treatment group of 13% who achieved FPG <

7.0 mmol/l and HbA1C < 6.2% off therapy after 2 years of follow-up observed in the Dixon *et al*[9] trial, after adjusting for the longer duration of diabetes since diagnosis in participants in our trial (≤ 5 years versus < 2 years). Assuming a 10% remission rate in controls, a type 1 error of 5% and a one-sided test, a total sample size of 100 participants (50 per treatment group) is estimated to provide 80% power to show an absolute risk increase of >29% in the induction of diabetes remission between treatment groups (effect size > 2.9) and 90% power to show an absolute risk difference of >34% (effect size > 3.4).

8.0 Drug Supply

The following supply of sitagliptin/metformin will be provided for each patient: Sitagliptin/metformin 50/500 mg po OD for 4 days, then 50/500 mg po bid for 4 days, then 50/850 mg po bid for 4 days, then 50/1,000 mg po bid for 72 days. Insulin glargine will be purchased and dispensed through local pharmacies.

9.0 Adverse Events

Information on the following clinical events will be collected in all study participants during the trial:

a) Death (and cause of death as determined by a physician);
b) Non-fatal coronary disease events (non-fatal myocardial infarction or angina resulting in hospitalization or emergency room admission);
c) Non-fatal cerebrovascular disease events (non-fatal stroke or transient ischemic attack diagnosed by a physician);
d) Heart failure resulting in hospitalization or emergency room admission;
e) Resuscitated cardiac arrest or life-threatening arrhythmia (including documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity);
f) Cardiogenic shock diagnosed by a physician;
g) Diabetic ketoacidosis or hyperglycemic hyperosmolar state diagnosed by a physician;
h) Documented new fractures;
i) Symptomatic and severe hypoglycemic events;
j) Hospital admissions or emergency room visits (and reasons for admissions/visits).

Participants will be monitored for adverse events and overdoses from the time of randomization until the end of follow-up. Only those serious adverse events that investigators believe to be related to the study drugs will be recorded as serious adverse events. For non-serious adverse events, only those adverse events resulting in a change in dose (including temporary withholding) of any of the study medications (insulin glargine, metformin and sitagliptin) will be documented on case report forms.

10.0 References

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3. Li Y, Xu W, Liao Z et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. Diabetes Care 2004;27(11):2597-2602.

4. McFarlane SI, Chaiken RL, Hirsch S, Harrington P, Lebovitz HE, Banerji MA. Near-normoglycaemic remission in African-Americans with Type 2 diabetes mellitus is associated with recovery of beta cell function. Diabet Med 2001;18(1):10-16.

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7. Weng J, Li Y, Xu W et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371(9626):1753-1760.

8. Canadian Diabetes Association Clinical Practice Guidelines. 2013. https://www.diabetes.ca/clinical-practice-education/clinical-practice-guidelines.
Ref Type: Online Source

9. Dixon JB, O'Brien PE, Playfair J et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA 2008;299(3):316-323.

Table 1. Schedule of visits and assessments in the intervention group (I), control group (C), and both groups (X).

	Weeks after randomization																			
	-1	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	7	8	9	10	11	12
Eligibility criteria	X																			
Informed consent	X																			
Randomization		X																		
Start study medication		I																		
Stop diabetes medications																				X
Clinic visit	X	X		I		I		I		I		I		X		I		I		X
Telephone follow-up			I		I		I		I		I		I		I		I		I	
Dietary advice		X		I						I						I				I
Physical activity advice		X		I						I						I				I
Diabetes education		X																		
Adherence to medications and side effects			I	I	I	I	I	I	I	I	I	I	I	X	I	I	I	I	I	X
Review SMBGs			I	I	I	I	I	I	I	I	I	I	I	X	I	I	I	I	I	X
Anthropometrics*	X	X				I		I		I		I		X		I		I		X
Blood pressure	X	X								I				X		I				X
Physical activity and food frequency questionnaires	X																			X
ECG	X																			
Fasting serum for storage**		X																		
FPG		X																		
ALT	X																			
Serum Cr and urine BhCG***	X																			
HbA1C	X																			X
Two glucose profiles****														X						X
Standard 75 g OGTT*****																				
Return to standard glycemic care if hyperglycemia relapse identified																				

BhCG - beta human chorionic gonadotrophin, FPG - fasting plasma glucose, OGTT - oral glucose tolerance test, SMBG - self-monitoring of capillary blood glucose.

*Anthropometrics will include height and weight at screening visit, and weight, waist circumference, and hip circumference at subsequent visits.

**Fasting serum sample will be taken for storage at baseline and at 16 weeks. Participants taking glucose-lowering medications will be asked to hold them for 48 hours prior to these tests unless fasting capillary glucose rises above 12 mmol/L.

***Urine BhCG will be measured in women with childbearing potential.

**** Two six-point glucose profiles will be collected on separate days. Each six-point glucose profile will include pre-meal and 2-hour post-meal SMBG readings taken on the same day.

*****Standard 75 g OGTT will be performed in the morning, after overnight fasting. Blood samples for glucose will be drawn at 0 minutes and 120 minutes after administration of the 75 g oral glucose load. The OGTT will be performed at 24 weeks after randomization. Participants taking glucose-lowering medications will be asked to hold them for 48 hours prior to the test unless fasting glucose rises above 12 mmol/L.

	Weeks after randomization													
	12.5	16	20	24	28	32	36	40	44	48	52	56	60	64
Eligibility criteria														
Informed consent														
Randomization														
Start study medication														
Stop diabetes medications														
Clinic visit		X		X			X			X				X
Telephone follow-up	X		X		X	X		X	X		X	X	X	
Dietary advice		I												
Physical activity advice		I												
Diabetes education														
Adherence to medications and side effects	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SMBGs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anthropometrics*		X		X			X			X				X
Blood pressure		X		X			X			X				X
Physical activity and food frequency questionnaires				X			X			X				X
ECG														
Fasting serum for storage**		X												
FPG		X												
ALT		X		X										
Serum Cr and urine BhCG***														
HbA1C				X			X			X				X
Two glucose profiles****														
Standard 75 g OGTT*****				X										
Return to standard glycemic care if hyperglycemia relapse identified	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BhCG - beta human chorionic gonadotrophin, FPG - fasting plasma glucose, OGTT - oral glucose tolerance test, SMBG - self-monitoring of capillary blood glucose.
*Anthropometrics will include height and weight at screening visit, and weight, waist circumference, and hip circumference at subsequent visits.
**Fasting serum sample will be taken for storage at baseline and at 16 weeks. Participants taking glucose-lowering medications will be asked to hold them for 48 hours prior to these tests unless fasting capillary glucose rises above 12 mmol/L.
***Urine BhCG will be measured in women with childbearing potential.
**** Two six-point glucose profiles will be collected on separate days. Each six-point glucose profile will include pre-meal and 2-hour post-meal SMBG readings taken on the same day.
*****Standard 75 g OGTT will be performed in the morning, after overnight fasting. Blood samples for glucose will be drawn at 0 minutes and 120 minutes after administration of the 75 g oral glucose load. The OGTT will be performed at 24 weeks after randomization. Participants taking glucose-lowering medications will be asked to hold them for 48 hours prior to the test unless fasting glucose rises above 12 mmol/L.