Obesity Treatments to Improve Type 1 Diabetes. The OTID trial Protocol for obesity treatments to improve Type 1 Diabetes. The OTID trial

Ebaa Al-Ozairi  
Dasman Diabetes Institute

Kavita Narula (✉ k.narula@nhs.net)  
Imperial College London  https://orcid.org/0000-0002-7453-9039

Alexander D. Miras  
Ulster University

Etab Taghadom  
Dasman Diabetes Institute

Abeer El Samad  
Dasman Diabetes Institute

Jumana Al Kandari  
Dasman Diabetes Institute

Anas Alyosef  
Amiri Hospital

Anant Mashankar  
Dasman Diabetes Institute

Werd Al-Najim  
Imperial College London

Carel W. le Roux  
Imperial College London

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Abstract

• Background

The guidelines of the American Diabetes Association and European Association for the Study of Diabetes suggest that patients with obesity type 2 diabetics, and chronic kidney disease need either glucagon-like peptide 1 receptor analogues or sodium-glucose cotransporter-2 inhibitors. If neither achieve metabolic control, then the recommendation is to combine both drugs. The evidence base for combining glucagon-like peptide 1 receptor analogues and sodium-glucose cotransporter-2 inhibitors are not well researched, and hence the impact of the guidelines are limited. The aim of this randomized controlled trial is to test the impact of the combination of glucagon-like peptide 1 receptor analogues / sodium-glucose cotransporter-2 inhibitors on body weight and kidney damage, in patients with type 1 diabetes and chronic kidney disease. In addition, we will explore associated changes in metabolic pathways with each of the treatments used in this randomized controlled trial.

• Methods

In this 6-month randomized control trial, 60 participants aged between 21–65 years, with a body mass index above 25kg/m2 and type 1 diabetics with chronic kidney disease will be randomized to receive one of five possible treatments 1) Standard care (control), 2) glucagon-like peptide 1 receptor analogues alone, 3) sodium-glucose cotransporter-2 inhibitors alone, 4) combination of glucagon-like peptide 1 receptor analogues and sodium-glucose cotransporter-2 inhibitors, 5) combination of glucagon-like peptide 1 receptor analogues and sodium-glucose cotransporter-2 inhibitors with intensive lifestyle advice. The primary objective will be the percentage change in total body weight from baseline at 6 months. The secondary objectives are to compare change in glycaemia, blood pressure, dyslipidaemia, albuminuria, proportion of participants reaching weight loss of ≥ 5%, ≥ 10% and ≥ 15%, change in BMI (kg/m2) from baseline and change in waist circumference (cm). All the experiments will be conducted at the Dasman Diabetes Institute after approval from the local research and ethics committee.

• Discussion

The present randomized controlled trial aims to investigate the impact of the combination of glucagon-like peptide 1 receptor analogues and sodium-glucose cotransporter-2 inhibitors on body weight and kidney damage in patients with type 1 diabetes mellitus and chronic kidney disease, as well as exploring associated changes in metabolic pathways with each of the treatments used. This study addresses the current gap in the evidence base regarding the combination of these two drugs, which is particularly relevant given the American Diabetes Association and European Association for the Study of Diabetes guidelines recommending their combined use for patients with obesity, type 2 diabetes, and chronic kidney disease who do not achieve metabolic control with either drug alone.

Trial registration

ClinicalTrials.gov Identifier: NCT0539030
# Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

<table>
<thead>
<tr>
<th>Title (1)</th>
<th>Obesity Treatments to Improve Type 1 Diabetes. The OTID trial.</th>
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<tbody>
<tr>
<td>Trial registration (2a and 2b).</td>
<td>ClinicalTrials.gov Identifier: Nmissing CT0539030.</td>
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<tr>
<td>Funding (4)</td>
<td>The trial has received funding from Ministry of Health (MOH) Kuwait and Kuwait foundation for advancement of Science (KFAS).</td>
</tr>
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</table>
| Author details (5a) | 1Dasman Diabetes Institute, Kuwait City, Kuwait.  
2Department of Medicine, College of Medicine, Kuwait University, Kuwait  
3Department of Metabolism, Digestion and Reproduction, Imperial College London, UK.  
4School of Medicine, Ulster University, UK  
5Amiri Hospital, Ministry of Health, Kuwait  
6Diabetes Complications Research Centre, Conway Institute, University College of Dublin, Dublin, Ireland. |
| Name and contact information for the trial sponsor (5b) | Ulster University, Cromore Rd, Coleraine BT52 1SA |
| Role of sponsor (5c) | The study will be conducted in accordance with the current approved protocol, International Conference on Harmonisation guidelines for Good Clinical Practice (ICH GCP), relevant regulations and the Standard Operating Procedures (SOP) and quality management procedures of sponsor, and host organizations. As part of the quality management process a monitoring plan will be developed by the sponsor. The sponsor will carry out all study monitoring. A documented monitoring log and audit trail will be maintained throughout the lifetime of the study. |

## Introduction

### Background and rationale (6a)
As the obesity pandemic continues unabated, one can expect to see an increase in complications in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D), such as chronic kidney disease (CKD)\(^{(1)}\). As a result, early deaths will rise, preceded by an increase in kidney failure, requiring dialysis and renal transplantation\(^{(2)}\). Intensive diabetes therapy aimed at achieving near normoglycemia reduces the risk of complications of T1D\(^{(3)}\). However, glycaemic control remains suboptimal and difficult to achieve with insulin therapy alone, and only a minority of adults with T1D achieve appropriate glycated haemoglobin (HbA1c) goals. Many patients with T1D suffer from hypoglycaemia and weight gain whilst trying to achieve target HbA1c\(^{(4)}\).

The guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) suggest that patients with obesity, T2D, and CKD need either glucagon-like peptide 1 receptor analogues (GLP1RA) or sodium-glucose cotransporter-2 inhibitors (SGLT2i). If neither achieve metabolic control, then the recommendation is to combine both drugs\(^{(5)}\). The evidence base for combining GLP1RA and SGLT2i are not well developed, and hence the impact of the guidelines are limited. We will significantly contribute to this proof by distinguishing discrete metabolic pathways or not, triggered by GLP1RA and SGLT2i combinations. Such a discovery has the potential to change clinical practice.

GLP1RAs are now widely used in T2D, for its metabolic actions which include augmenting glucose-stimulated insulin release, inhibition of glucagon secretion, and slowed gastric emptying. GLP1RAs induce weight loss and in patients with T2D reduce major cardiovascular disease events. These benefits may also extend to patients with T1D particularly those with residual detectable levels of C-peptide\(^{(6)}\).

SGLT2i are glucose-lowering agents that exert their therapeutic activity independently of insulin by facilitating glucose excretion through the kidneys. However, this simple renal mechanism that results in sustained glucose urinary loss leads to more complex indirect metabolic effects. First, by reduction of chronic hyperglycaemia and attenuation of glucose toxicity, SGLT2i can improve both insulin secretion by beta cells and peripheral tissue insulin sensitivity\(^{(7)}\). A meta-analysis of 13 studies concluded that SGLT2i as an add-on treatment to insulin injections facilitate glycaemic control with a decreased insulin dose. SGLT-2i resulted in improvements in glycemia control, decreases in HbA1c, fasting plasma glucose, urinary glucose excursion values, and better effects on non-glucose-related targets, such as bodyweight loss\(^{(8)}\).

A meta-analysis of 1913 patients in 7 clinical trials with T2D suggests that GLP1RA and SGLT2i combination therapy had greater reduction in weight of 2.6 kg, HbA1c of 0.6%, and systolic blood pressure of 4.1 mmHg compared to GLP1RA alone and a greater reduction of weight by 1.8 kg, HbA1c by 0.9%, and systolic blood pressure by 2.7 mmHg compared to SGLT2i alone. The studies were not adequately powered to examine CKD or mortality\(^{(9)}\).

Additional analysis of Canagliflozin Cardiovascular Assessment Study (CANVAS) in patients with obesity, T2DM, and CKD used randomized treatment by subgroup interaction to compare the effects of
Canagliflozin versus placebo across subgroups defined by baseline use of GLP1RA or not. There were 10,142 patients, of whom 407 (4%) used GLP1RA at baseline. The subgroup of patients with GLP1RA and SGLT2i combinations had the best outcomes as regards to weight loss, glycaemic improvements, and blood pressure changes compared with the other 3 subgroups (i) no GLP1RA or SGLT2i, (ii) only GLP1RA, and (iii) only SGLT2i. This was the first evidence of a potential synergistic effect of combining GLP1RA and SGLT2i, although there are no trial data specifically designed to describe the effects of this combination. This study together with the ADA and EASD guidelines advising clinicians to consider combining these drugs, makes an urgent case for better mechanistic understanding. Identification of such discrete pathways will be a breakthrough.

The aim of this randomized controlled trial (RCT) is to test the impact of the combination of GLP1RA and SGLT2i on body weight as well as on kidney damage, in patients with T1D and CKD. In addition, we will explore associated changes in metabolic pathways with each of the treatments used in the RCT.

**Objectives**

The aim of the present study is to compare the clinical effectiveness of patients receiving:

- Standard care (control)
- GLP1RA only
- SGLT2i only
- Combination of GLP1RA and SGLT2i
- Combination of GLP1RA, SGLT2i and intensive lifestyle changes.

The primary objective will be the percentage change in total body weight from baseline at 6 months. The secondary objectives are to compare change in glycaemia, blood pressure, dyslipidaemia, albuminuria, proportion of participants reaching weight loss of ≥ 5%, ≥ 10% and ≥ 15%, change in BMI (kg/m2) from baseline and change in waist circumference (cm).

**Trial design**

The OTID study is an open-label, randomized controlled clinical trial in people aged between 21–65 years, who have a BMI above 25kg/m2, and have T1D with CKD. The trial will be conducted at Dasman Diabetes Institute (DDI) in Kuwait. The total duration of participation of follow-up will be 6 months.

**Methods: Participants, interventions and outcomes**

**Study setting**
The study used the SPIRIT reporting guidelines (12). All the trial activities will be conducted at DDI after approval from the local research and ethics committee. Potentially eligible patients will be identified by the clinical care team during routine care and invited for screening in outpatient settings. They will be given the patient information leaflet, if the patient expresses an interest in participating, they will be given a minimum of 48 hours to consider their participation.

**Eligibility criteria (10)**

**Inclusion Criteria**

To be considered eligible to participate in this study, a patient must:

- Be aged between 21–65 years
- Have a BMI ≥ 25kg/m2
- Have established diagnosis of T1D (per ADA 2022 definition/criteria) for at least 1 year before screening visit
- Insulin treatment for T1D may be either via any Food and Drug Administration approved Continuous subcutaneous insulin infusion pump (CSII) for at least 6 months prior to screening visit or via multiple daily insulin injections. All participants must be stable on insulin doses/ regimen for at least 3 months
- Have established diagnosis of CKD 1–4
- Able to give informed consent

**Exclusion Criteria**

Participants will be excluded if:

- They have been treated with GLP1RA or SGLT2i within the last 3 months and/or have a history of GLP1RA or SGLT2i intolerance
- Diagnosis of T2D or any other type of diabetes (other than type 1)
- Treatment with anti-obesity drugs within 12 weeks prior to randomization
- Significant changes in the lifestyle (Diet or exercise pattern in within 3 months of the screening visit)
- Any self-reported changes (gain or loss) in body weight > 5% within 3 months of screening visit
- eGFR ≤ 15 mL/min/1.73m2
• Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using or willing to use adequate contraceptive methods during the study period

• Experienced diabetic ketoacidosis within 6 months of screening visit

• Experienced sever hypoglycaemia within 6 months of screening visit

• Any of the following laboratory values at screening (liver chemistry > 3X upper limit of normal, high triglyceride (> 5.7 mmol/L)

• Have terminal illness or are not primarily responsible for their own care

• Any other significant disease or disorder which in the opinion of the investigator, may either put the participants at risk or may influence the result of the study or the participant’s ability to participate

• Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone > 6 mIU/litre or < 0.4 mIU/litre

• Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)

• Personal history of non-familial medullary thyroid carcinoma

• History of chronic pancreatitis or idiopathic acute pancreatitis

• Amylase levels three times higher than the upper normal range

• Obesity induced by other endocrinologic disorders (e.g. Cushing’s syndrome)

• Current or history of treatment with medications that may cause significant weight gain, within 12 weeks prior to randomization, including systemic corticosteroids (except for a short course of treatment, i.e. 7 – 10 days), atypical antipsychotic and mood stabilizers (e.g. clozapine, olanzapine, valproic acid and its derivatives, and lithium)

• Initiation of antidepressants during the last 12 weeks

• Previous surgical treatment for obesity (excluding liposuction if performed > 1 year before trial entry)

• History of other severe psychiatric disorders

• History of known or suspected abuse of alcohol and/or narcotics

• History of major depressive episode during the last 2 years

• Simultaneous participation in other clinical trials of investigational drugs, lifestyle or physical activity interventions. Patients will only be able to take part following participation in a previous clinical trial after
a wash-out period of 16 weeks

• History of dementia or cognitive impairment

Who will take informed consent? {26a}

The screening and consent procedures are performed at the Baseline Visit. Patients will attend an appointment with a healthcare professional at the study site. The healthcare professional will check their eligibility to participate, explain in detail what the study involves and answer any questions they may have. Full written informed consent to participate will then be obtained. The person obtaining informed consent will be a suitably trained and a competent healthcare professional who, in the opinion of the Principal Investigator (PI), is able to give a full, unbiased explanation of the study, including benefits and risks, to the potential participant. The person obtaining consent will also have been named in the delegation log of staff as undertaking this duty and will be approved as study personnel by the relevant governance procedures. Each participant will also have a copy of the consent form and patient information leaflet; a copy will be placed in their hospital medical records and the original copy held in the site Masterfile.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable

Interventions

Explanation for the choice of comparators {6b}

Sixty participants will be randomized to receive one of five possible treatments:

1. usual standard care,
2. GLP1RA alone,
3. SGLT2i alone,
4. the combination of GLP1RA and SGLT2i,
5. the combination of GLP1RA, SGLT2i and intensive lifestyle changes.

Intervention description {11a}

i) Control (standard)

Participants in the Control (Standard Care) care arm will follow the best standard medical care provided at Dasman Diabetes Institute following the international guidelines for 6 months. In brief, this will involve intensive insulin therapy to maintain good glycaemic control. The treatment is complex and highly individualized, but the three main components of T1D management include: insulin therapy, blood glucose monitoring and carbohydrate counting as per the Dose Adjustment For Normal Eating (DAFNE)
training program which patients have received. In addition, patients will also have their hypertension and dyslipidaemia treated while being monitored for symptoms and signs of micro- and macrovascular complications of T2D. These participants will not be started on GLP1RA or SGLT2i medication during the trial.

ii) GLP1RA alone

Participants in the GLP1RA will be prescribed either Liraglutide up to a dose of 3.0mg daily or Semaglutide up to a dose of 1.0mg subcutaneous injection weekly, depending on their preference. The dose and titration will follow the usual clinical practice. The treatment will last 6 months.

iii) SGLT2i alone

Participants in the SGLT2i group will be prescribed Dapagliozin 5-10mg once daily for 6 months.

iv) Combination of GLP1RA and SGLT2i

Participants in the combination GLP1RA and SGLT2i group will be prescribed Liraglutide up to a dose of 3.0mg daily or Semaglutide up to a dose of 1.0mg subcutaneous injection weekly plus Dapagliozin 5-10mg for 6 months. The medications will be started simultaneously.

v) Combination of GLP1RA, SGLT2i and intensive lifestyle changes

Participants in the combination GLP1RA, SGLT2i and intensive lifestyle group will be prescribed Liraglutide 3mg once daily or Semaglutide 1mg once weekly subcutaneous injection plus Dapagliozin 5-10mg together with an intensive lifestyle approach for 6 months. Based on age, gender, CKD status, each patient will receive meal plans delivered by a registered dietician. This will involve dietary advice to reduce energy intake with calorie deficit of 500 calories per day (and may include a period of partial or total meal replacement), accompanied by participation in a physical activity program, both supported by behavioral change techniques with regular professional contact.

**Criteria for discontinuing or modifying allocated interventions {11b}**

Certain circumstances will necessitate stopping the study for a particular participant. Adverse event review and other safety/acceptability assessments will provide the information for the study clinician to withdraw the participant and/or discontinue the treatment drug at any time during the trial.

Participants may withdraw consent from the study before study completion if they decide to do so, at any time and for any reason. If a participant decides to withdraw from the study, this will be recorded in the study records. They will be contacted to thank them for their participation, and to inform them that the data collected up to the time point they withdrew will be included in the study analysis and that they will not be contacted again with regards to this study if they so wish. They will not be asked to attend further
visits against their will. Furthermore, we will emphasize that their standard care will not be affected by their withdrawal from this study.

Participants will be withdrawn from this study by the research team as agreed by the PI if:

- They are diagnosed with a terminal illness
- The PI, Sponsor and or study clinician deem it unsafe for continuation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations or Good Clinical Practice
- They are considered to be lost to follow-up
- Loss of capacity during participation in research
- Treatment with medications that can interfere with the studies

For participants who fail to return to the site, the research team should make reasonable effort to re-contact the participants (e.g., contacting participant's family or family doctor, reviewing available registries or health care databases) and to determine his/her health status, including at least his/her vital status. Attempts to contact such participants must be documented in the participant's records (e.g. times and dates of attempted telephone contact, receipt for sending a registered letter).

Attempts will be made to assess the primary outcome on all participants whether or not they were compliant and in those who have who have discontinued the treatment. Temporary discontinuation of the treatment drugs may be considered by the PI because of suspected adverse events. A rationale (e.g. severe nausea and vomiting, other gastrointestinal symptoms) must be given in writing by the PI.

Re-initiation of treatment may be done at a lower dose, under close and appropriate clinical/and or laboratory monitoring. For all temporary treatment discontinuations, the duration of treatment discontinuation should be recorded by the research team when considered as confirmed.

Permanent treatment discontinuation is any treatment discontinuation from the PI or the participant, not to re-expose the participant to the allocated drug treatment at any time. Participants may withdraw from treatment with the investigational drug if they decide to do so, at any time and for any reason. The PI may also decide to withdraw a participant from the study based on an inability of the subject to adhere to the obligations of the study or for the safety of the participant. Items that will lead to permanent discontinuation in the study include:

- Pregnancy
- Episode of acute pancreatitis and breast malignancy (only for participants in GLP1RA groups)
- They repeatedly violate or are non-compliant with the protocol
- Where GLP1RA or SGLT2i doses are not tolerated by the participant
- Any other contraindication to the study medication which the PI determines to require permanent treatment discontinuation.
All efforts should be made to document the reasons for treatment discontinuation, and this should be documented in the case report form (CRF).

**Strategies to improve adherence to interventions {11c}**

Participants randomized to GLP1RA and/or SGLT2i arm will be instructed to take their subcutaneous injections or tablets whilst continuing their usual medication. Participants will be given specific instructions to adhere to the titration policy of GLP1RA. GLP1RA and/or SGLT2i will be prescribed and provided to participants for the duration of the trial.

Participants will be asked to return all unused investigational products and vials/packages to the pharmacy at each study visit. Compliance and concordance with GLP1RA and/or SGLT2i will be evaluated and discussed at each study visit based upon tolerability and returned pens. Participants will be defined as treatment compliant if they actually receive at least 70% of planned doses.

**Relevant concomitant care permitted or prohibited during the trial {11d}**

Only the patient in the control group will continue to receive regular standard care during the trial.

Participants in the GLP1RA group will be prescribed either Liraglutide up to a dose of 3.0mg daily or Semaglutide up to a dose of 1.0mg subcutaneous injection weekly, depending on their preference. The dose and titration will follow the usual clinical practice.

Participants in the SGLT2i group will be prescribed Dapagliflozin 5-10mg once daily for 6 months.

Participants in the combination GLP1RA and SGLT2i group will be prescribed Liraglutide up to a dose of 3.0mg daily or Semaglutide up to a dose of 1.0mg subcutaneous injection weekly plus Dapagliflozin 5-10mg for 6 months. The medications will be started simultaneously.

Participants in the combination GLP1RA and SGLT2i and intensive lifestyle group will be prescribed Liraglutide 3mg once daily or Semaglutide 1mg once weekly subcutaneous injection plus Dapagliflozin 5-10mg together with an intensive lifestyle approach for 6 months.

**Provisions for post-trial care {30}**

Post-trial care will be standard care as per Dasman Diabetes Institute clinical pathways. Compensation for harm will be provided by Dasman Diabetes Institute as per research standard operating procedures.

**Outcomes {12}**

**Primary Outcome**

The primary outcome will be the percentage change in total body weight at 26 weeks.

**Secondary Outcomes**
Secondary outcomes at 26 weeks will be:

- Proportion of participants reaching total body weight loss of $\geq 5\%$, $\geq 10\%$ and $\geq 15\%$
- Change in waist circumference
- Change in HbA1c
- Change in systolic blood pressure
- Change in diastolic blood pressure
- Change in lipid profile
- Change in albumin creatinine ratio

**Participant timeline {13}**

**Invitation of Eligible Patients**

A study clinician will determine the eligibility of potential participants in the clinic and approach suitable participants.

**Screening and Consent Visit**

The screening and consent procedures are performed at the Screening Visit. Patients will attend an appointment with a healthcare professional at the study site. The healthcare professional will check their eligibility to participate, explain in detail what the study involves and answer any questions they may have. Full written informed consent to participate will then be obtained.

**Screening visit**

A member of the research team will record in the screening visit CRF the participant demographics, medical and surgical history, medication history, and perform measurement of anthropometrics (height, weight, and waist circumference), blood pressure and pulse rate for all the participants in line with site's own SOPs. The research team member will arrange for standard laboratory testing (HbA1c, fasting glucose, thyroid stimulating hormone, Free T4, lipid profile, renal profile, liver function test and 24-hr urine creatinine, microalbumin and sodium), and will also provide participants with urine containers and instructions for the collection of the 24-hour urine sample for creatinine clearance test.

A member of the research team will schedule all procedures for Visit 1 to be performed on the same day. This will include the phlebotomy appointment, Dual-Energy X-ray Absorptiometry (DEXA) scan appointment, Magnetic Resonance Imaging (MRI) of the liver appointment, 24-hour Blood Pressure (BP) monitor appointment and the intermittently scanned Continuous Glucose Monitoring (isCGM) appointment.

Before Visit 1, all participants will receive two reminder calls to remind them of the date and time of their appointment, as well as instructions for urine collection. Participants must also fast for at least 8 hours
before the phlebotomy appointment and will be asked to avoid taking Calcium, Iron and Vitamin D supplements for 48 hours before the radiological procedure.

**Visit 1**

All participants are provided with blood glucose meters and urine ketone strips to be used for additional monitoring. Instructions will be provided to report any symptoms of hypoglycaemia and measurements of ketones if they were to exhibit any symptoms of diabetic ketoacidosis. Visit 1 includes five procedures:

**Phlebotomy Procedure – Visit 1**

All participants will perform this procedure on the same visit day. Blood for biochemistry and the 24 hours urine container will be collected at Visit 1 and after six months from the intervention at Visit 2. Blood and urine samples for omics data will be collected for all patients.

**DEXA Scan – Visit 1**

All participants will have a DEXA scan performed on the same visit day, to measure fat mass and fat free mass at Visit 1 and after six months from the intervention at Visit 2. Total fat mass, total lean mass, arm lean mass, leg lean mass and trunk lean mass will be measured using a GE Lunar iDXA scanner.

**Magnetic resonance imaging (MRI) of the liver – Visit 1**

All participants will have a liver MRI test on the same visit day or within a window of 10 days, to measure fat and fibrosis in the liver at Visit 1 and after six months from the intervention at Visit 2. Liver fat will be quantified by MRI. Proton Density Fat Fraction (PDFF) technique is used to quantify the liver fat. The MRI studies are performed on a 1.5 Tesla scanner (Signa Artist, GE Medical systems, USA). The PDFF calculation is done with IDEAL-IQ sequence provided by the manufacturer (Slice thickness 8mm, echo time 6 ms, echo repetition time 13.3 ms). This sequence is designed to separate water and triglyceride fat by acquiring six different echoes on the IDEAL (Iterative Decomposition of water & fat with Echo Asymmetry and Least square estimation) technique with simultaneous T2* correction (Idilman IS, Tuzun A, Savas B, et al. Quantification of liver, pancreas, kidney & vertebral body MRI-PDFF in non-alcoholic fatty liver disease. Abdom Imaging 40:1512–1519 (2015)). The Fat Fraction of the liver tissue was calculated by placing four rounded Regions of Interest (ROI) of an average area of 400 square millimetre in segments II/III, V/VI, VII and VIII of liver. It was decided to obtain an average Fat Fraction value of the four readings as the final observation. An additional reference ROI was also placed in the anterior abdominal subcutaneous fat (Idilman IS, Aniktar H, Idilman R, et al. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. Radiology 267:767–775 (2013)). Magnetic Resonance Elastography (MRE) of liver is performed to assess the liver parenchymal stiffness. This is performed with MR TOUCH sequence (Slice thickness 8 mm, echo time 1 ms, echo repetition time 50 ms) provided by the manufacturer (Signa Artist, GE Medical systems, USA). The Acoustic Driver System (Resoundant Inc. Rochester, MN, USA) is used for the impulse generation. In addition, T2 weighted axial
sequence was obtained for the upper abdomen to look for any significant incidental findings. Any significant incidental findings observed were conveyed to the PI for necessary remedial action.

24-hour BP Monitoring – Visit 1

This procedure is optional and will be conducted at Visit 1 and after six months from the intervention at Visit 2.

isCGM Procedure -Visit 1

All participants will be offered FreeStyle Libre (FSL) 1 sensors for six months duration from the start of the intervention till the end of the study. The FSL sensors were installed and connected to the FreeStyle LibreLink App then linked to the cloud-based diabetes management LibreView system.

Electronic Bluetooth Weight Scales – Visit 1

All participants will be offered eufy Smart Scale C1 and connected to the EufyLife App that automatically syncs all weight results to the app via Bluetooth.

Randomisation – Visit 1

Randomisation will be carried out by the Sponsor at Ulster University (UU) after Visit 1 and after confirmation of the participants eligibility is received by the research team at Dasman Diabetes Institute. Randomisation will be carried out via www.sealedenvelope.com

Follow-up visits

For the majority of participants follow-up occurs as part of usual care in the DDI, with only two specific study visits added at the start of the study (Visit 1) and at 6 months after the study started (Visit 2). Adjustments for each participants are made at discretion and clinical judgement of the investigator, as appropriate for that individuals based on the individuals glycaemic data. All changes of insulin to carbohydrate ratio and/or insulin sensitivity factor will be documented in CRF. For the subgroups randomized to Group 02 (GLP1RA alone), Group 04 (GLP1RA and SGLT2i combination), and Group 05 (GLP1RA, SGLT2i and intensive lifestyle treatment), the empty medication pens, foil packaging and medication compliance will be checked regularly for all participants from the intervention start date until the end of the study.

Definition of End of Trial

The end of the study is defined as the last participant’s last visit.

Sample size (14)
The sample-size calculation assumed at least a 10-percentage-point difference in the mean percentage weight reduction from baseline at 26 weeks for the combination of GLP1RA and SGLT2i as compared with standard care, a common standard deviation of 10%, and a dropout rate of 17%. Using these parameters, we will have 90% power to detect statistically significant differences between the groups at \( \alpha = 0.05 \). This estimation was based on the available evidence for body weight reduction using Liraglutide 3mg daily \(^{13}\) or Semaglutide 1mg weekly \(^{14}\), Dapagliflozin 10mg daily \(^{15}\) and the weight loss achieved at the DDI when standard care is provided in people with T1D.

**Recruitment** \(^{15}\)

Patients will be identified and approached by their usual clinical care team. They will be given the patient information leaflet, if the patient expresses an interest in participating, they will be given a minimum of 48 hours to consider their participation. All the trial activities will be conducted at DDI after approval from the local research and ethics committee.

**Assignment of interventions: allocation**

**Sequence generation** \(^{16a}\)

Randomization will be carried out by the Sponsor at Ulster University (UU) on the first visit after screening and after confirmation of the participants eligibility is received by the research team at DDI. Randomization will be carried out via www.sealedenvelope.com

**Concealment mechanism** \(^{16b}\)

Randomization will be carried out via www.sealedenvelope.com. The investigator will text the participant’s code to the website and receive the randomisation back directly from the website in order to maintain the integrity of the concealment mechanism. The allocation will be announced to the patient at the same visit.

**Implementation** \(^{16c}\)

Randomization will be carried out via www.sealedenvelope.com, a central randomisation system. The investigator will text the participant’s code to the website and receive the randomisation back directly from the website in order to maintain the integrity of the concealment mechanism. The allocation will be announced to the patient at the same visit.

**Assignment of interventions: Blinding**

**Who will be blinded** \(^{17a}\)

This is an open label trial. The only staff that will be blinded will be the data analysts.

**Procedure for unblinding if needed** \(^{17b}\)
Participants and research team will not be blinded.

**Data collection and management**

**Plans for assessment and collection of outcomes (18a)**

The sponsor is responsible for the data management of this study including quality checking of the data. All participant data relating to the study will be recorded on CRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Documentation must be completed in source documents or participant’s medical record. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to the Sponsor for data verification and validation purposes. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone). Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site staff are accurate, complete and verifiable from source documents.

**Plans to promote participant retention and complete follow-up (18b)**

Drop-out rates in similar studies run at DDI are approximately 10%. The research staff form excellent relationships with participants who enjoy taking part in research and contributing to the generation of new knowledge. Research staff are enthusiastic and motivate participants. Regular patient-centered events will be organised to increase engagement and participant retention. This approach creates a “belonging to a group” feeling and has been very effective in previous studies.

**Data management (19)**

Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only. No direct identifiers from the participant are transferred to the Sponsor. The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Data that are transcribed into the CRF from source documents must be consistent with the source documents, or the discrepancies must be explained.

**Confidentiality (27)**

The PI agrees to provide reliable data with all information requested by the clinical study protocol in an accurate and legible manner, according to the instructions provided and to ensure direct access to source documents by Sponsor representatives. With any data transfer, particular attention will be paid to provide confidentiality to the subjects’ data.
Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only. No direct identifiers from the participant are transferred to the Sponsor. The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use (33)**

Samples will be collected through venesection or urine sampling and stored in -80 freezers at the DDI. No genetic analyses will be performed.

**Statistical methods**

**Statistical methods for primary and secondary outcomes (20a)**

The primary outcome is % total body weight loss from baseline at 26 weeks and will be compared between groups based on a hierarchical model.

(i) Difference in % total body weight loss between the combination of GLP1RA and SGLT2i group vs. the standard care group. If statistically significant the following comparison will be made.

(ii) Difference in % total body weight loss between the combination of GLP1RA and SGLT2i group vs. the SGLT2i alone group. If statistically significant the following comparison will be made.

(iii) Difference in % total body weight loss between the combination of GLP1RA and SGLT2i group vs. the GLP1RA alone group. If statistically significant the following comparison will be made.

(iv) Difference in % total body weight loss between the combination of GLP1RA and SGLT2i group vs. the combination of GLP1RA and SGLT2i and intensive behavioral modification group.

The primary analysis will be based upon the complete case population. This is defined as all randomized participants who have data available for the outcome being analyzed, according to the study group to which they were randomized at baseline. Secondary outcomes measured at 26 weeks will also be analyzed based upon the complete cases population. Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided.

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous
measurements assessed over time will be a mixed model for repeated measures (MMRM), with terms of treatment, visit, and treatment-by-visit interaction, and baseline measurement as a covariate.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Logistic regression will be used to examine the treatment difference in binary efficacy outcomes if there is a need to adjust for covariates. Otherwise, Fisher’s exact test will be used to examine the treatment difference in categorical outcomes.

Summary statistics for discrete count measures will include sample size, mean, standard deviation, median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures. Data on treatment adherence, safety (including adverse events), and treatment satisfaction will be summarized and tabulated.

**Interim analyses (21b)**

No interim analyses planned.

**Methods for additional analyses (e.g. subgroup analyses) (20b)**

No subgroup analyses will be conducted.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data (20c)**

All efforts will be made to prevent the occurrence of missing data. Nevertheless, it is anticipated that withdrawals will occur and hence there will be missing data on primary and secondary efficacy endpoints. We will use mixed-effects modelling, which naturally accounts for missing data assuming that data are missing at random. The number of participants with missing data per variable and reasons will be reported as recommended.

**Plans to give access to the full protocol, participant level-data and statistical code (31c)**

Access to the protocol is available through clinicaltrials.gov. Access to participant level data and statistical code will be available upon request.

**Oversight and monitoring**

**Composition of the coordinating centre and trial steering committee (5d)**

The trial steering committee will be composed of Professor Carel le Roux, Dr Ebaa Al-Ozairi, Professor Alex Miras. They will meet every 3 months to discuss the progress of the trial and design future strategy.

**Composition of the data monitoring committee, its role and reporting structure (21a)**
A DMC is not needed for this trial as all treatments are routinely available for people with T1DM in Kuwait. The aim of this trial is to compare these treatments and their combination. The analyses of the study will take place by independent analysts who will be blinded to treatment allocation.

**Adverse event reporting and harms (22)**

Throughout the OTID study, all the reported Adverse Events (AE), Adverse Reactions (AR), Severe Adverse Events (SAE), Serious Adverse Reaction (SAR) and other unintended effects of trial interventions or trial conduct will be collected and assessed. Members of the research team will ask the participants about AEs at each study visit and will complete the participant AE form, which will be a continuous log so as to capture end dates, and the study SAE log.

During and following a patient’s participation in the study, the PI will ensure that adequate medical care is provided to the participant for any AE, including clinically significant laboratory values related to the trial. All serious adverse events and all non-serious adverse event classified as severe or possibly/probably related to the study treatment will be followed-up until the participant has recovered, recovered with sequelae, or fatal and until all queries have been resolved.

**Frequency and plans for auditing trial conduct (23)**

The sponsor will audit the trial every 6 months according to its standard operating procedures.

**Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) (25)**

All changes to the study protocol will be reviewed by the research ethics committee and then reported to the sponsor and funder. All protocol changes will be communicated to and through ClinicalTrials.gov.

**Dissemination plans (31a)**

Upon completion of the study, all participants will be informed for the results of the study. The results of the study will be presented in national and international meetings and will be submitted for publication to the relevant peer-reviewed journals. Acknowledgement of any supporting organizations, including funders, will be included.

**Discussion**

Not applicable

**Trial status**

Recruitment started on 1st February 2023 and the last patient last visit is expected by 1st December 2023.
Abbreviations

ADA - American Diabetes Association
AE - Adverse Events
AR - Adverse Reactions
BP - Blood Pressure
CANVAS - Canagliflozin Cardiovascular Assessment Study
CKD - Chronic kidney disease
CRF - Case report form
CSII - Continuous subcutaneous insulin infusion
DAFNE - Dose Adjustment For Normal Eating
DDI - Dasman Diabetes Institute
DEXA - Dual-Energy X-ray Absorptiometry
EASD - European Association for the Study of Diabetes
FMTC - Familial medullary thyroid carcinoma
FSL - FreeStyle Libre
GLP1RA - Glucagon-like peptide 1 receptor analogues
HbA1c - Glycated haemoglobin
ICH GCP - International Conference on Harmonisation guidelines for Good Clinical Practice
IDEAL - Iterative Decomposition of water & fat with Echo Asymmetry and Least square estimation
isCGM - intermittently scanned Continuous Glucose Monitoring
MEN 2 - Multiple endocrine neoplasia type 2
MMRM - Mixed model for repeated measures
MOH - Ministry of Health
MRE - Magnetic Resonance Elastography
Authors’ contributions

EO and CWIR conceived the concept, obtained funding and supervising the conduct of the study, KN and ADM wrote the manuscript, ADM, ET, AA, AM, JAK, AES, WAN have provided intellectual input to the conduct of the trial or are executing the trial on a day-to-day basis.

Funding

This manuscript is part of the Obesity Treatments to Improve Type 1 Diabetes Trial (The OTID trial). The trial has received funding from Ministry of Health (MOH) Kuwait and Kuwait foundation for advancement of Science (KFAS). The funder has no role in the design of this study and will not have any role during execution, analyses, interpretation of data or submission of outcome.
Availability of data and materials {29}

The authors of this manuscript will have access to the final trial dataset. There are no contractual agreements that limit such access for investigators.

Ethics approval and consent to participate {24}

All experimental protocols have been approved by the Dasman Diabetes Institute Ethics committee (Reference no. RAHM 2021009). The research will be performed in accordance with the Declaration of Helsinki. Participants will take part in the study after having provided written informed consent.

Consent for publication {32}

Not applicable

Competing interests {28}

ADM has received research funding from the National Institute for Health and care Research, Medical Research Council, Jon Moulton Charity Trust, Fractyl, Novo Nordisk, Fractyl and Randox. ADM has received honoraria for educational events from Novo Nordisk, Astra Zeneca, Currrax, Boehringer Ingelheim Screen Health and GI dynamics. These funders were not involved in this study. The remaining authors declare no conflict of interest. The communication reflects the author's view and DDI Kuwait is not responsible for any use that may be made of the information contained therein.

Authors’ information (optional)

Not applicable.

References


5. Buse J, Wexler D, Tsapas A et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European


Figures
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Figure 1

Template for the schedule of enrolment, interventions and assessments for OTID.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.docx
- SPIRITchecklist1.docx