COVER PAGE

Official Study Title: The Effect of GLP1 Receptor Agonists on Physical Function, Body Composition, and Biomarkers of Aging in Older Overweight/Obese Adults with Insulin Resistance

NCT number: NCT05786521

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Form CT
UTHSA Clinical Trial Description

This form is not mandatory. Other documents are acceptable if equivalent information is provided.

UTHSCSA Tracking Number *(internal use only)*	20220256HU	**1. Original Version Date**	08-31-22
		1.1. Revision Date(s) *add rows as needed*	2.0

2. Background

Briefly discuss the important literature relevant to the trial and that provides background for the trial. Include the importance of the trial and any relevant treatment issues or controversies.

Approximately 25% of older adults in the U.S. have Type 2 Diabetes (T2D) and nearly 50% have prediabetes. The mechanisms that cause age-related glucose intolerance and diabetes are unknown, but age-dependent decreases in β-cell function and insulin sensitivity are thought to be important in deterioration of glucose homeostasis with age. There are also changes in body composition with age that can contribute to insulin resistance with age, including: (1) redistribution of fat from peripheral and subcutaneous to a central location, and (2) loss of lean muscle mass . Thus, most older adults have some degree of insulin resistance and mechanisms that contribute to insulin resistance become more pronounced with aging.

The usual comorbidities associated with diabetes are recognized as cardiovascular, renal, and neuropathic diseases; however, there are physical function and body composition changes which occur which impact aging outcomes. A meta-analysis by Wong et showed that those with diabetes had an increased risk of mobility disability, defined by walking speed, chair stand, and balance tests, compared to those without diabetes (risk ratio=1.51, 95%CI 1.38-1.64). These physical changes have also been seen in those with prediabetes. Over 12 years, those with prediabetes compared to normoglycemia had an increased predicted trajectory of chair stand time ($p<0.05$), decreased walking speed ($p<0.01$) and an accelerated disability progression ($p<0.01$). In multiple longitudinal studies, older adults with diabetes lost more lean mass compared to those without diabetes. Further, the decline of physical function as measured by various assessments (balance, walking speed, balance) and sarcopenia, decline of lean body mass, are predictive of nursing home admission and death .

Inflammation is one of the key mechanisms underlying aging and age-related diseases. Chronic inflammation contributes to aging through several complex pathways. One pathway is cellular senescence, which contributes to normal aging, but also to the burden of low-grade chronic inflammation through activation of a wide range of growth factors, cytokines and other inflammatory factors. Higher levels of inflammation markers, interleukin (IL)-6 and C-reactive protein (CRP), have been demonstrated in individuals with insulin resistance as well as T2D, and are also predictors of frailty in older adults.

GLP1 receptor agonists are generally considered second line treatment for patients with T2D, but this class of medications maybe considered first-line in patients who are at high risk for cardiovascular disease or already have a history of cardiovascular disease. GLP1 receptor agonists increase insulin and decrease glucagon in response to hyperglycemia and suppress appetite likely mediated through actions on receptors in the hypothalamus and other areas of the central nervous system. Although weight loss is one of the benefits of this class, there is concern that the weight loss observed with GLP1 receptor agonist use is accompanied by loss of lean mass in addition to fat mass, which is especially concerning in an older adult population who have age-related sarcopenia. A review of the effect of GLP1 receptor agonists on body composition showed, as expected, a total body weight loss but the breakdown of weight loss from lean body and fat mass varied significantly between the studies. Some showed an increase in lean body mass while other showed that a significant portion of the weight loss came from lean body mass, up to 65.2%, in those treated with GLP1 receptor agonists T2D. Interestingly in rodent models, GLP1 receptor agonists have shown to have beneficial effects on skeletal muscle atrophy. A meta-analysis showed an improvement of the

pro-inflammatory milieu in patients with T2D treated GLP1 receptor agonists compared to placebo or other T2D medications with a significant change of CRP (-0.54mg/L, 95% CI -0.7- -0.34), tumor necrosis factor alpha (-0.39, 95% CI -0.62 - -0.15), and adiponectin (0.30, 95% CI 0.12-0.49). Although there are known cardiovascular and weight management benefits of GLP1 receptor agonists outside of their ability to treat hyperglycemia, information about physical function is understudied especially in older adults. Use of GLP1 agonists is rapidly increasing, but research in older adults is very limited. This pilot work will be an important first step in examining the potential usefulness of GLP1 receptor agonists in older adults to improve glycemic control, as well as physical function and lean mass.

3. Objectives and Endpoints *All data points collected in the study should support an objective or have a regulatory purpose.*
Complete the table – add rows as needed.

3.1. Objective(s) *Clearly and concisely define the primary and secondary outcomes.*	**3.2. Endpoint** *Clearly define the endpoints. (endpoints are the basis for concluding that the objective has been met).*	**3.3. Justification for Endpoint** *Briefly explain why the endpoint(s) were chosen.*
Aim 1: To conduct a pilot study to examine the effect of GLP1 receptor agonists on physical function and body composition in older overweight/obese adults with prediabetes or well controlled diabetes. Aim 2: To examine the impact of GLP1 receptor agonists on biomarkers of aging (cellular senescence and inflammation) in older overweight/obese adults with prediabetes or well controlled diabetes.	Aim 1: Any change in -Short physical performance battery (SBBP) -Handgrip strength -6 minute walking distance -BMI -Body composition (lean body mass to fat mass) Aim 2: -Markers of cellular senescence and inflammation in muscle, adipose, and blood	GLP1 receptor agonists are an FDA-approved class of drugs for the treatment of T2D which lead to improvement in adiposity but possibly at the risk of significant decline on lean body mass. Additionally, there is a lack of studies to determine if these changes are associated with a significant change in functional status. Therefore, Aim 1 will address the specific hypothesis that the GLP1 receptor agonist semaglutide will improve physical function (SPPB, handgrip strength, walking speed) and body composition (BMI, lean body mass to fat mass ratio) compared to standard of care. Diabetes is known to be pro-inflammatory state that can promote cellular senescence. GLP1 receptor agonists have shown positive improvement of inflammatory makers but this has not been studied extensively in older adults. Therefore, Aim 2 will test the hypothesis that the GLP1 receptor agonist semaglutide (by improving glycemia and adiposity) will decrease markers of cellular senescence and inflammation in muscle, adipose tissue and blood.

4. Rationale
Briefly state the reason for conducting the clinical trial.

The results of this study will provide useful information which could influence the treatment algorithm for older adults with prediabetes or T2D. Currently, pharmacological intervention for older adults with prediabetes is not widely recommended although has been done in clinical trials with resultant reduction in diabetes onset . Further, older adults with diabetes who are otherwise healthy may not have medical management (i.e., drug therapy) added until glycemic goals are unmet (HbA1c >7.0-7.5%), which may have detrimental, lasting effects on aging muscle. If positive, our results would support the use of GLP1 receptor agonists in older adults with prediabetes or in well controlled diabetes earlier in the disease course to halt the progression of physical function decline and improve biomarkers of aging. Therefore, this knowledge will contribute to future studies in this area that will allow for geroscience-guided therapy for prediabetes and T2D in older adults to extend healthspan.

To minimize the risk of weight loss, we will enroll participants who meet the indication for GLP1 receptor agonist therapy for weight management in the presence of at least one comorbid condition which for this study will be prediabetes or diabetes (BMI ≥ 27.0, HgbA1c ≥ 5.7). We will have an upper limit for HgbA1c of 7.5% because at this time most clinicians would start or intensify medical therapy. We will have a BMI upper limit of 40.0 for ability to use DXA.

5. Study Design

5.1. Number of Groups/Arms	2	**Group name(s)**	(1) Medication and lifestyle (2) Lifestyle alone

5.2. Overall Design
Select all applicable

☒	**Randomization**	☐	**Cluster Randomized**				
☐	**Group-Sequential**	☐	**Adaptive Design**				
☐	**Parallel Design**	☐	**Placebo-Controlled**				
☐	**Superiority**	☐	**Equivalence**	☐	**Non-inferiority**		
Device	☐ Pilot	☐	Pivotal	☐	Post-Approval		
Drug/Biologic	☒ Phase 1	☐	Phase 1/2	☐	Phase 2	☐	Phase 2/3	☐	Phase 3	☐	Phase 4

☒	**Dose escalation**	*If yes, details →*	0.25mg weekly for 4 weeks, then 0.5mg weekly for 4 weeks, then 1mg weekly for 12 weeks. If unable to tolerate a higher dose then will adjust titration schedule.
☐	**Dose ranging**	*If yes, details →*	
☐	**Sub-studies**	*If yes, details →*	

5.3. Other Design Details: This will be a 20 week open label, randomized control trial. The study will start after approval from UT Health San Antonio IRB department. Subjects will be consented and then screened for eligibly before randomization into either the lifestyle or lifestyle plus study drug arm. All study visits will be performed at Barshop Clinical Research Unit.

6. Study Population

6.1. Study Population(s) Label/Name *To add more populations – select a row, copy & paste*	**6.2. Identify the criteria for inclusion** *The criteria that every potential participant must satisfy, to qualify for study entry.* All individuals in this study population must meet all of the inclusion criteria in order to be eligible to participate in the study	**6.3. Identify the criteria for exclusion** *The characteristics that make an individual ineligible for study participation.* All individuals in this study population meeting any of the exclusion criteria at baseline will be excluded from study participation.
Overweight/obese community dwelling older	1) Men and post-menopausal women 2) Age ≥ 65 years	1) Impaired renal function (GFR ≤ 29) 2) Hematocrit ≤ 33

adults with prediabetes or T2D.	3) All ethnic groups 4) BMI ≥ 27.0 kg/m^2 5) HbA1c 5.7-7.5%, fasting glucose ≥ 100, 7) Community – dwelling 8) At PI discretion, participant is willing/able to comply with the protocol requirements	3) Thyroid-stimulating hormone≥ 7 with an abnormal free T4 4) Immunodeficiency 5) Use of medications known to affect glucose homeostasis besides metformin (metformin is allowed) 6) History of cardiovascular events 7) Poorly controlled blood pressure (systolic blood pressure >170, diastolic blood pressure >95) 8) Active inflammatory, autoimmune, infectious, hepatic, gastrointestinal, malignant, or uncontrolled psychiatric disease 9) stable body weight (<5% change during the 3 months prior to screening) 10) personal or family history of medullary thyroid cancer (MTC) 11) personal or family history of Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) 12) previous history of pancreatitis, 13) ECG with QTc prolongation (QTc >470 ms in men or >480 ms in women) or evidence of ischemic changes 14) Diabetic Retinopathy 15) Allergy to semaglutide or any of the ingredients in the drug formulation 16) Type 1 Diabetes 17) BMI ≥ 40 kg/m^2 18) Current tobacco or illicit drug use
6.4. **Will screen failures be allowed to <u>re-screen</u> at a later date?**	☐ **No** ☒ **Yes** *If yes, describe criteria below ↓* Will be able to be rescreened after 12 weeks	

7. Study Intervention(s) being tested or evaluated

This can include prevention, diagnostic or therapeutic interventions (e.g., drug or device) or educational, health services or basic science interventions (e.g., educational program, health care delivery model, or examining basic physiology)

Semaglutide (Ozempic)

8. Protocol-Directed procedures, items, services or tests

List all procedures directed by the study plan - including items or services provided as part of routine or conventional care and those needed to diagnosis or treat research related complications.

Important Note – The protocol directed procedures listed must match those in the Schedule of Activities (attachment)

8.1. Drugs *(trade and generic, dosage, route of administration)*

Control group-lifestyle alone group: Subjects will meet with a dietician throughout the study to discuss lifestyle counseling based on recommendation in the diabetes prevention program.

Intervention group- Semaglutide+ lifestyle : Ozempic , starting at 0.25mg once a week for 4 weeks then 0.5mg once weekly for 4 weeks followed by 1.0mg once a week, subcutaneously as tolerated. Additionally, they will meet with a dietician through the study to discuss lifestyle counseling based on recommendation in the diabetes prevention program.

8.2. Devices

8.3. Biologics

8.4. Laboratory Tests

Clinical labs include CBC, lipid panel, CMP, TSH, PT/INR, PTT, and HbA1c will be done to determine eligibility and follow the effect of treatment.

8.5. Imaging Procedures

8.6. Other Research Procedures *(e.g., other safety and efficacy assessments.)*

-ECG: ECG will be performed to examine for QTc prolongation or other cardiac issues contraindicated for exercise

-Vitals and anthropometric measurements: Weight will be measured at all visits to track BMI, heart rate, and blood pressure

-Functional assessments of SPPB, 6 minute walking distance, and grip strength will be done at baseline and at end of study to determine the effect of the intervention.

-Questionnaires of SF-12 (quality of life) and CNAQ (appetite assessment) will be done at baseline and at end of study determine the effect of the intervention.

-DXA: body composition will be determined by DXA at baseline and end of study to determine the effect of the intervention

-Assays of cellular senescence and senescence-associated secretory phenotype (SASP) in muscle, adipose and blood will be conducted in the Barshop Institute, including β galactosidase staining, PCR (IL-6, TNFα, p16, p21, TLR4, and MCP1), and immunoassays (CRP, ADAMTS13, CCL3, CCL4, CCL5, CCL17, CCL22, FAS, GDF15, GDNF, ICAM1, IL15, IL6, IL7, IL8, MMP2, MMP9, OPN, PAI1, SOST, TNFR1, TNFα, and VEGFA). These will be done at the beginning and end of study to determine the effect of study intervention.

8.7 Attach a Schedule of Activities (SOA) Excel File [Download the Template here: *Schedule of Activities*]	*Check to indicate that the SOA Excel File is attached → X* ☐

9.	**Preparation/Handling/ Storage/Accountability of Investigational Drug, Biologic, or Device**
☐	*N/A - This study does not include any investigational products (e.g. drugs, devices or biologics)*
☐	*N/A - An Investigator Brochure is attached*
☐	***X N/A - A Drug/Device Manual is attached- The FDA prescribing insert for both Wegovy and Ozempic which are the trade names for semaglutide.***

9.1. Acquisition and accountability

State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.

Semaglutide will be provided by the pharmacy to Barshop staff. Barshop staff will then dispense medication and log in appropriate visits. Unused medication will be returned to pharmacy for disposal.

9.2. Formulation, Appearance, Packaging, and Labeling

Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

SEMAGLUTIDE DOSAGE FORMS AND STRENGTHS:
Injection: 2 mg/1.5 mL (1.34 mg/mL) of semaglutide as a clear, colorless solution available in:
- Pre-filled, disposable, single-patient-use pen that delivers 0.25 mg (for treatment initiation) or 0.5 mg (for maintenance treatment) per injection.
-Pre-filled, disposable, single-patient-use pen that delivers 1 mg (for maintenance treatment) per injection.

We will only be using Ozempic in this study. Since Ozempic and Wegovy are the same active ingredient used at different doses (Wegovy starts at 0.25mg once a week and increases up to 2.4mg once a week), we have add the indications for Wegovy.

INDICATIONS AND USAGE
OZEMPIC (semaglutide) is a glucagon-like peptide 1 (GLP-1) receptor agonist
indicated as:
• an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
• to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular
disease .

WEGOVY (semaglutide) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced calorie diet and increased physical
activity for chronic weight management in adult patients with an initial body mass index (BMI) of
• 30 kg/m2 or greater (obesity) or
• 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Manufactured by: Novo Nordisk A/S DK-2880 Bagsvaerd Denmark

9.3. Product Storage and Stability

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

We will be providing participants Ozempic in the intervention arm.

Prior to first use, OZEMPIC should be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze OZEMPIC and do not use OZEMPIC if it has been frozen. Can be used until expiration on pen.

After first use of the OZEMPIC pen, the pen can be stored for 56 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Do not freeze. Keep the pen cap on when not in use. OZEMPIC should be protected from excessive heat and sunlight.

9.4. Preparation

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section. For devices, include any relevant assembly or use instructions.

NA –Medication will be obtained from MedPlus pharmacy (may change based on cost of medication). The medication will be labeled “for investigational use only” in addition to the usual labeling of medication, dose and instructions.

9.5. Risks and Benefits

Risks
Risk of Thyroid C-cell Tumors

Semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician [see Boxed Warning and Warnings and Precautions (5.1)].
Pancreatitis
There is a potential risk for pancreatitis. Instruct will be given to patients to discontinue OZEMPIC promptly and contact the study team if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting).
Diabetic Retinopathy Complications
Inform patients to contact the study team immediately if changes in vision are experienced during treatment with OZEMPIC
Never Share an OZEMPIC Pen Between Patients.
Advise patients that they must never share an OZEMPIC pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne.
Dehydration and Renal Failure
There are potential risk of dehydration due to gastrointestinal adverse reactions and precautions should be taken to avoid fluid depletion. There is a potential risk for worsening renal function and participants will be informed about the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs.
Hypersensitivity Reactions
Participants will be informed to stop taking OZEMPIC and seek medical advice promptly if symptoms of hypersensitivity reactions occur.

Most common side effects of semaglutide administration are nausea, vomiting, diarrhea, abdominal pain and constipation which usually decrease over time in the majority of patients.

Possible Benefits

- Improved glycemic control in type 2 diabetic participants
- Beneficial weight loss leading to decreased BMI
- Possible improvement of pro-inflammatory milieu
- If positive, study results would support the use of GLP1 receptor agonists in older adults with prediabetes or in well controlled diabetes earlier in the disease course to halt the progression of physical function decline and improve biomarkers of aging. Therefore, this knowledge will contribute to future studies in this area that will allow for geroscience-guided therapy for prediabetes and T2D in older adults to extend healthspan.

10. Study Intervention Additional Details

10.1. Measures to Minimize Bias: Randomization and Blinding

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

The study is unblinded. Participants (N=20) will be randomized into two groups using a randomization table to receive either (1) semaglutide plus standard lifestyle recommendation or (2) standard lifestyle recommendations alone.

10.2. Study Intervention Compliance

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).

Participants will have four visits while on study medication to discuss whether they remain eligible and if there are any adverse events to report and to verify adherence to protocol. They will be asked to bring in their medication to study visits if randomized to the study drug arm to determine adherence.

10.3. Permitted Concomitant Therapy

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints).

Use of medications known to affect glucose homeostasis besides metformin (metformin is allowed) is a part of exclusion criteria. Other medications will be allowed.

10.4. Rescue Medicine

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions.

☒ *: N/A, no rescue medicine*

11. Study Intervention Discontinuation

11.1. Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or re-challenging with study intervention.

Study medication will be discontinued in the event of a severe allergic reaction or development of an episode of pancreatitis. If minor GI (nausea, abdominal pain, vomiting, etc) side effects occur, then the study medication titration will be modified based on symptoms and severity of these anticipated side effects.

11.2. Continued Follow-up Discontinuation of Study Intervention

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems involving risks to subjects or others (UPIRSOs).

If participants discontinue study medication, then we will follow up with participants to determine resolution of symptoms and relationship with medication.

12. Statistical Considerations

12.1. Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

We hypothesize that semaglutide will improve physical function (SPPB, handgrip strength, walking speed) and body composition (BMI, lean body mass to fat mass ratio) in those with prediabetes and well controlled diabetes. It is expected that the pleiotropic effects of GLP1 receptor agonists will also result in improvement of aging biomarkers including cellular senescence and inflammation in muscle and adipose tissue.

12.2. Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

The effect of GLP1 receptor agonists on aging-related biomarkers and physical function in is not known. For this pilot study, we will screen up to 100 potentially eligible participants to achieve a target of 20 completers. More candidates will be screened if attrition (est. 20%) requires it. The data generated through this study will guide sample size and power calculations for future studies.

12.3. Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

Population for analyses will be divided in the two arms (1) medication and lifestyle and (2) lifestyle alone

12.4. Statistical Analyses

Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses

Experimental results will be expressed as means ± SE. Comparisons of means between all the groups will be done by ANOVA for repeated measures. Associations, within a group, between aging-related biomarkers vs. healthspan outcomes will be determined by Pearson's correlation. For tests of correlation coefficients between groups, we will use the Fisher's Z transformation. We will also determine the relationship between aging-related biomarkers vs healthspan outcomes, by using multiple regression analysis.