UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

RESEARCH PROTOCOL OPEN ACCESS

# Research Protocol: Effects of GLP-1 Therapy on Skeletal Muscle Health Across Stages of Type 2 Diabetes

Ben Mei-Dan, BSc Student [1]*

[1] Department of Biology, Duke University, Durham, North Carolina, United States, 27708

Corresponding Author: ben.mei-dan@duke.edu

**Abstract**

**Introduction:** Glucagon-like peptide-1 (GLP-1) agonists are key components of type-2 diabetes mellitus (T2DM) treatment due to their role in improving insulin secretion, inhibiting glucagon release, promoting lipid metabolism, and enhancing satiety. Recent studies have highlighted the possible drawback that comes with intended weight loss: muscle loss. This study seeks to better understand the significance of this muscle loss in terms of strength, function, and total mass lost in T2DM individuals with comorbid obesity.

**Methods:** A 20-week treatment trial will investigate lean mass changes with the administration of GLP-1 agonists in 3 T2DM cohorts: insulin-reliant, metformin-reliant, and prediabetic groups, and their respective controls. Overall health analysis will occur through metrics such as total mass, lean mass, grip strength, $^{31}$P-MRS, quality of life questionnaires, HbA1c, and lipid panel. Through these, a holistic view on GLP-1 effectiveness, its relationship to unintended lean mass loss, and its health implications as a whole can be gained.

**Results:** A relatively linear relationship between severity of T2DM and/or greater BMI and lean mass lost – both proportionally and absolutely – is anticipated. Similarly, the greater the severity of T2DM the more significant the decrease in muscle strength and function is predicted. Inversely, the most significant improvements in terms of HbA1c and lipid panel will be in the greater severity T2DM cohorts. Overall quality of life and patient experience will increase noticeably across all three treatment groups with respect to controls with slightly less increases with more severe T2DM.

**Discussion:** This study improves GLP-1 usage guidelines through an investigation of the treatment over different populations. It exhibits the first literature utilizing $^{31}$P-MRS to gain insight on muscle function decreases across diabetic patients undergoing GLP-1 therapy. Possible co-treatments may be recommended in future studies to limit the lean mass lost in already susceptible populations.

**Conclusion:** In conclusion, GLP-1 agonists demonstrate significant effects on lean mass, muscle strength, muscle function, and diabetic biomarkers, with the severity of T2DM varying the extent of the effects. While quality of life improvements are noticeable, the impact of GLP-1 treatment on muscle dynamics highlights complex interplay between muscle preservation and intended weight loss.

**Keywords:** GLP-1 receptor agonist; type 2 diabetes; lean mass; weight loss; muscle function; skeletal muscle; obesity

## Introduction

A growing body of literature is supporting new and seemingly more effective weight loss treatments being developed within the obesity realm, known as glucagon-like peptide-1 (GLP-1) receptor agonists [1]. These recently introduced, diverse diabetes and obesity treatments are taking both the scientific and commercial world by storm and are the focus of this work.

Type 2 Diabetes Mellitus (T2DM) is a condition that affects over 400 million people globally, with an ever-rising incidence [2]. It is characterized by insulin resistance and declining ß-cell function. ß-cells within the pancreas are specialized cells designed to secrete insulin and C-peptide, among other hormones [3]. The T2DM severity "spectrum" is generally characterized by specific target ranges for three tests: fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and Hemoglobin A1c (HbA1c) (Figure 1) [4]. These tests assess various aspects of an individual's ability to maintain glycemic control; FPG assesses the body's maintenance of blood glucose after a fast, OGTT assesses the body's ability to process glucose by measuring the body's reaction to a glucose challenge, and HbA1c assesses the general trends of blood glucose over a 2-3 month period through the percentage of glycated hemoglobin [4, 5].

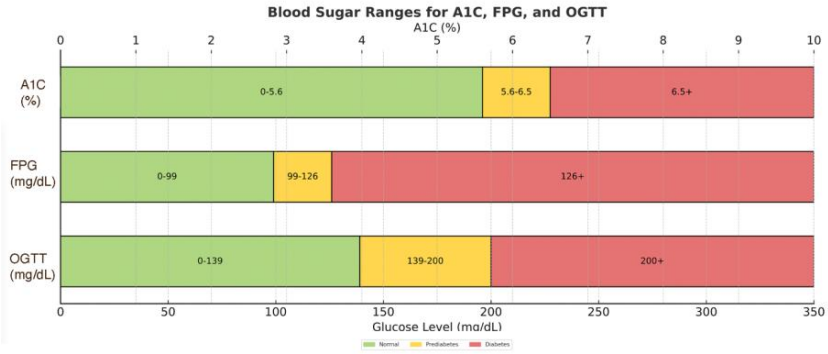


**Figure 1.** Diagnostic ranges for blood glucose and A1C used to define normoglycemia (green), prediabetes (yellow), and diabetes (red). A1C (%) is shown on the y-axis, with the corresponding x-axis shown on the top. FPG, and, OGTT (mg/dL glucose) are shown on the y-axis with the corresponding x-axis shown on the bottom. Created with Python. Hb*A1C – hemoglobin A1C, FPG – fasting plasma glucose; OGTT – oral glucose tolerance test.*

First line pharmacokinetic treatment for T2DM is metformin, a drug that suppresses liver glucose production and improves insulin sensitivity within muscle and fat cells [6]. The goal of this treatment is to lower overall blood glucose levels without directly affecting insulin. This is done through the hepatic gluconeogenesis inhibition and activation of AMP-activated protein kinase (AMPK) – an enzyme that plays a role in cellular metabolic homeostasis [6]. As T2DM progresses, the pancreas loses its ability to produce enough insulin through ß-cell dysfunction [7]. Exogenous insulin therapy becomes necessary at this stage, and the T2DM is generally considered advanced and irreversible through lifestyle modifications [7]. Blood sugar levels remain elevated and high metformin doses are no longer sufficient to manage hyperglycemic events [7]. Lifestyle changes such as increased physical activity and diet modifications are still crucial components of care, but can no longer solely manage the condition.

Recently GLP-1 agonists became a treatment for all severities of T2DM alike. GLP-1 is an endogenous gut hormone produced in the intestinal L-cells. It maintains glucose homeostasis through increasing glucose-dependent secretion of insulin whilst simultaneously suppressing glucagon stores [8]; this paired with activation of GLP-1 receptors in the brain slows the food digestion and increases satiety [9]. This discovery quickly prompted the testing and subsequent approval of the GLP-1 receptor agonist treatment for T2DM [1]. A growing body of evidence indicates that GLP-1 agonists promote significant weight loss with minimal side effects, making them a very effective and safe treatment for people suffering from obesity as well, for which they are also clinically indicated and approved [1].

Studies have highlighted that the rapid weight reduction may have the drawback of unintended muscle loss [10]. Skeletal muscle mass, strength, and function, all must be closely monitored in this patient population that already suffers from reduced levels of these crucial components [11]. Resistance training has been shown to counteract this decline through preservation and enhancement of muscle mass and strength, highlighting the importance of muscle-specific training during weight loss [12]. Patients with high risk of falls, frailty, low existing lean mass, and older diabetics all require elevated monitoring for muscle loss [13]. Since the muscle mass is crucial for metabolic function and glucose disposal, when it is eventually lost, metabolic function will decrease in these populations starting a downward spiral of reduced physical capacity and worsening glycemic control [14]. Muscle mass loss in older individuals and specifically in T2DM patients significantly increases the risk for sarcopenia [15]. It is of note that muscle mass includes skeletal muscle and some connective tissue while lean mass includes skeletal muscle, skin, organs, tendons, and body water [16].

This study seeks to better understand the significance of GLP-1 agonist-associated lean mass loss in patients with varying severities of T2DM and comorbid obesity. Patients will be subgrouped based on the accepted severity of T2DM: prediabetes (least severe), metformin-reliant T2DM (intermediate), and insulin-reliant T2DM (most severe). Allocation will be further discussed in methodology. While previous trials have focused on general glycemic trends and muscle loss in T2DM cohorts, they have yet to assess how these drugs affect muscle mass, strength, and function at different stages of the T2DM "spectrum" [17–21]. Understanding how GLP-1 agonists impact skeletal muscle mass across patients with varying T2DM severity can promote safe and effective usage of these drugs in varying diabetics. New clinical trials exhibit successful muscle mass retention and even growth during GLP-1 agonist induced weight loss with a new class of drugs entitled myostatin and activin inhibitors [22]. This work may offer further evidence to support adjunct treatments, such as exercise or these muscle conserving drugs, as necessary co-treatments when prescribing GLP-1 agonists by investigating the effect of GLP-1 agonists on lean mass, strength, and function across 3 distinct groups of T2DM patients w comorbid obesity.

## Methods

Trial Design

This trial is randomized, double-blind, parallel-group, placebo-controlled trial aimed at assessing the effects of GLP-1 receptor agonist therapy on lean mass, muscle strength and function, and metabolic parameters in T2DM individuals. Semaglutide is the most widely prescribed GLP-1 agonist, and will therefore be used for this study [23]. The trial will be conducted over 20 weeks, as it has been shown that most of the muscle mass lost in GLP-1 studies occurs in the first 15 weeks of treatment [24]. The randomization for group classification will be determined by a computer-generated sequence. Participants and outcome assessors will be blinded to group allocation. Baseline data will come from verification and categorization of participants as either diabetic or pre-diabetic based on the HbA1c.

### Participants

Participants will be enrolled with the inclusion criteria of a prediabetes or diabetes diagnosis and a body mass index (BMI) >30 kg/m$^2$. The 270 participants will be allocated into groups of 90 based on the following classification: pre-diabetics, metformin-dependent diabetics, and insulin-dependent diabetics. Each group of 90 will be randomly split into 3 groups of 30, one taking the GLP-1 agonist on top of their diabetes treatment, one taking a placebo GLP-1 agonist on top of diabetes treatment, and one staying as a control with only their diabetes. Additional inclusion criteria are as follows: age 18-65, diagnosed T2DM (confirmed with an HbA1c of 6.5-10.0%) or prediabetes (HbA1c of 5.6-6.5%), stable metformin and insulin usage (if applicable). Exclusion criteria include any current or past use of GLP-1 agonists, adjunct diabetes treatments, existing sarcopenia, myopathy or other neuromuscular conditions, past surgical obesity treatment, and uncontrolled hypertension [25].

### Dosing and Intervention

The three GLP-1 agonist groups will receive a weekly semaglutide via a subcutaneous injection of an initial 0.5 mg that increases by 0.5 mg every week until week 5, where the maintenance dose of 2.5 mg is kept constant. It will be administered by blinded study staff. The placebo group will receive saline injections within commonly recognized semaglutide syringes on a matched schedule. While resistance training remains a proven approach for improving muscle function and reducing muscle loss, this study seeks to isolate pharmacologic effects of GLP-1-specific mechanisms.

### Outcomes

The data collection will come from a monthly evaluation of the study's aims. Evaluations will take place at baseline and every 4 weeks following (Table 1). The primary outcome measured in this study is lean mass. This will be measured using a dual energy x-ray absorption (DEXA) scan that will approximate lean mass in the arms, legs, and trunk. A muscle strength and a function assessment, indicated by grip strength and phosphorus magnetic resonance spectroscopy ($^{31}$P-MRS) tests, respectively, will be performed. Hand grip strength testing remains an essential and validated proxy for assessing overall muscle strength [26]. $^{31}$P-MRS has become standard for tracking muscle function through an evaluation of muscle metabolism and mitochondrial function in a non-invasive reproducible fashion [27]. Key muscle metabolites are measured after muscle contraction to assess mitochondrial oxidative function and muscle bioenergetics [27]. To mitigate potential challenges with participant compliance and the technical demands of $^{31}$P-MRS, assessments will be aligned with pre-existing visits, participants will receive completion reminders, and missing data will be clearly reported. At each follow-up a lipid panel (total cholesterol, LDL-C, HDL-C, triglycerides, non-HDL-C), HbA1c, and homeostatic model assessment of insulin resistance (HOMA-IR) for insulin sensitivity rating will be taken. The HbA1c will be used to distinguish and properly place participants due to its ability to reflect average blood glucose markers over three months, providing a more stable indicator of long-term glycemic control as opposed to the acute tests (FPG & OGTT) [28], though the FPG will be used for the HOMA-IR. An Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) questionnaire will quantitatively reflect overall quality of life (QOL) and patient experience [29].

**Table 1.** Aims of Study and Measurement Schedule. Created with Word. Hb*A1c – hemoglobin A1C, DEXA – dual energy x-ray absorptiometry; $^{31}$P-MRS – phosphorus magnetic resonance spectroscopy; HOMA-IR – homeostatic model assessment of insulin resistance.*

| Outcome / Aim | Measurement Schedule (weeks) |
|---|---|
| Weight | Baseline, 4, 8, 12, 16, 20 |
| DEXA | Baseline, 4, 8, 12, 16, 20 |
| $^{31}$P-MRS | Baseline, 4, 8, 12, 16, 20 |
| Grip Strength | Baseline, 4, 8, 12, 16, 20 |
| Lipid Panel | Baseline, 4, 8, 12, 16, 20 |
| HbA1c | Baseline, 4, 8, 12, 16, 20 |
| HOMA-IR | Baseline, 4, 8, 12, 16, 20 |
| QOL Questionnaire | Baseline, 4, 8, 12, 16, 20 |

**Statistical Analysis Plan**

A 2-way analysis of variance will be used to compare mean changes in aims across groups while linear regression will assess associations between weight loss, glycemic outcomes, and changes in muscle parameters. It will be adjusted for baseline value, age, sex, and diabetes class. Subgroup analyses will also be run based on BMI classes. Statistical significance will be stated with an alpha rejection threshold of $\alpha = 0.05$; the sample size provides 90% power with approximately 30 participants per group (n=270). For the purpose of anticipated results, the placebo-controlled group will not be discussed as this can not be predicted.

**Anticipated Results**

Weight Loss

Control groups will likely maintain similar weight and lean mass as compared to baseline. Slight fluctuations in mass may occur in the metformin and insulin-dependent groups as their respective treatments play their role. Total weight loss is anticipated to be relative to baseline weight and proportional to T2DM severity. Therefore, the DEXA scan may reveal that the insulin-dependent groups will lose more lean mass proportional to their total mass lost compared to the metformin-dependent and prediabetic cohorts. Prior studies assessing lean mass change over 40-72 week ranges with semaglutide injections have decreased 2-13% [19, 30–32]. It is expected that the fraction of total mass lost that is lean mass will range in the 1.5-15.0% range, with the insulin group and/or higher starting BMI individuals likely to be closer to 15% and prediabetic groups and/or lower starting BMI individuals likely to be closer 1.5% [33].

**Muscle Strength and Function**

The prediabetic control group will likely maintain similar strength and function values as compared to baseline. The metformin and insulin dependent control groups, especially the latter, will likely experience a slight decrease in strength and function as their conditions progress [34]. Since insulin-dependent T2DM is considered a late-stage disease, the muscle insulin resistance is often severe and continually worsening [7]; therefore, the natural progression of T2DM will interplay within the control group and decrease grip strength and muscle energetic values over the 20-week period. Similar trends to lean mass will be observed – the more severe the diabetes, the greater the decrease of strength and function for the GLP-1 groups will be observed. The greater the baseline impairment of muscle energetics and strength the more likely the GLP-1 agonists will negatively affect overall muscle function. The negative effects of losing functional muscle fibers along with the minimization of muscle load could likely offset the gains from metabolic function and lead to possible functional decline [35]. Additionally, increased systematic insulin sensitivity does not always equate to improved mitochondrial function [36]. GLP-1 agonists will reduce muscle mass volume at greater rates with more severe T2DM, as aforementioned, and this equates to greater decreases in grip strength and muscle energetics. Grip strength testing will likely reveal a modest reduction in peak contraction force in all GLP-1 agonist treatment groups. $^{31}$P-MRS will likely reveal reduced phosphocreatine (PCr) recovery rates across all three treatment groups, indicating slightly impaired muscle energetics from GLP-1 therapy. The bioenergetics will decrease the most in efficacy in the insulin-dependent group as severe diabetes is associated with mitochondrial defects such as decreased mitochondrial density and impaired electron transport chain properties [37].

**Biomarkers and Diabetes**

All control groups will likely maintain stable diabetic biomarkers as their respective treatments hopefully maintain glycemic control homeostasis. The GLP-1 users are expected to show significant improvement in the HbA1c and the HOMA-IR tests throughout the timeframe with the improvements maintaining a relatively linear fashion, with plateaus beginning to occur at week 15. The more severe the diabetes, the greater the improvements expected in these tests; worse initial values for these tests exhibit greater room for improvement. Lipid panel improvements will be great across all groups as they improve with weight loss and appetite suppression caused by the agonists [1].

**Overall Quality**

Quality of life will remain relatively stable across all control groups. Muscle mass, strength, and function trends will invert for quality of life. The less severe the diabetes, the greater the improvements in QOL. In severe diabetes the significant weight loss and increased metabolic markers will be accompanied by decreased function, strength loss, and fatigue. Reduced appetite and natural breakdown of metabolites will diminish gains to QOL. Prediabetics will notice the greatest increase in QOL as there is the least disease burden and treatment may bring the group closer to a non-diabetic state, though all three groups will notice large increases in quality of life values.

**Discussion**

The anticipated findings suggest that GLP-1 agonists are effective in improving glycemic control and promoting total weight loss. However, an unwanted side effect that accompanies this GLP-1 agonist-induced weight loss is a measurable loss of muscle mass, strength, and function. Using $^{31}$P-MRS, the picture becomes more sophisticated, as the loss of muscle mass may be accompanied by altered muscle energetics – evidenced by slower PCr recovery times and reduced ATP levels. The decrease in functionality is likely to correlate with decreased grip strength. This emphasizes that GLP-1 agonists induce muscle changes that are not purely structural but also have functional implications.

The clinical relevance of maintaining skeletal muscle function is significant [10]. Muscle function in aging and diabetic populations is even more crucial, as these populations are pre-disposed to higher risks of sarcopenia and frailty which leads to osteoporotic elderly fractures and increased mortality rates [38]. If muscle function is expected to reduce substantially despite metabolic benefits, then long-term GLP-1 therapy may need to be reevaluated in T2DM populations for adjunct therapy possibilities. This study is among the first to propose the use of $^{31}$P-MRS to evaluate muscle bioenergetics in a T2DM GLP-1 study. This provides a mechanistic insight into how weight loss agents directly affect mitochondria and cellular pathways within the muscle [27]. This distinguishes between functional and structural muscle loss, and should be recommended in future studies regarding long-term prescription of GLP-1 agonists.

Potential mechanisms that underlie the findings of decreased muscle energetics and reduced grip strength are possible appetite suppression leading to reduced protein intake that eventually cascades to decreased muscle protein synthesis [39]. Reduced caloric intake also produces exercise intolerance making individuals less likely to exercise as it is more strenuous for them [40]. More severe obesity likely comes with more absolute and proportional fat loss as there are higher initial fat reserves to draw from. Conversely individuals with lower BMI's are at higher risk to lose more muscle mass proportional to total mass lost [41]. Recent work has demonstrated the efficacy of combining GLP-1 agonists with myostatin/activin-A inhibitors for the preservation (and even increase) of muscle mass in non-human primates, optimizing body composition statistics while on these agonists [22].

## Limitations and Future Directions

Availability of $^{31}$P-MRS is limiting, leading us to certain imaging centers which may delay participant recruitment. However, the anticipated results support the underlying idea that muscle function loss accompanies lean mass loss, emphasizing the importance of function-based assessments in future studies. Skeletal muscle function can change and vary based on age, sex, and baseline activities [42]. As well, inter-individual differences in treatment response can play a factor depending on previous experience with muscle hypertrophy and atrophy [43]. Additionally, the study duration does not leave time to observe long-term trends associated with GLP-1 agonist treatment. While the majority of weight loss occurs in the first 15 weeks of therapy [24], it would be helpful to observe long-term data associated with GLP-1 agonists to see how muscle function continues to shift once weight loss has slowed significantly. This study terminated with the cessation of GLP-1 agonist administration; possible future studies should investigate the effects of a treatment termination on all previously discussed aims in the context of rebound weight gain [44, 45].

Future studies should explore the co-administration of GLP-1 agonists with protein supplementation [46], anabolic agents (e.g. myostatin inhibitors) [22], or simply resistance training [46], to possibly limit the aforementioned functional. It may be helpful to investigate whether GLP-1/GIP co-agonists exhibit the same muscle effects, and if trends are similar on smooth and/or cardiac muscle to understand GLP-1 more broadly. Only once these broader ideas are understood a holistic view of GLP-1 therapy can be gained to individualize treatment to the needs of patients.

## Conclusions

Type 2 Diabetes Mellitus exists on a severity "spectrum," ranging from prediabetes all the way to latter stage insulin-dependent diabetes. The purpose of this study was to examine the effects of GLP-1 therapy on lean mass, muscle strength, muscle function, diabetic biomarkers, and quality of life across a range of diabetics in a population with comorbid obesity. The loss of lean mass has exhibited significance within the clinical realm and concerns about body composition shifts in weight reduction have prompted the need for its investigation. This research proposal expects to find significant lean mass reductions and shifts in overall body composition across all treatment groups. The more severe the diabetes and/or starting BMI, the more severe the lean mass reductions (absolutely and proportionally), muscle strength reductions, and function reductions will likely be. The more severe diabetics will likely have less improvements in quality of life as weight reductions are offset by fatigue and significant muscle and function results; they will have the best improvements in lipid and diabetic biomarkers though, as they have the most improvement from the get-go. While GLP-1 agonists offer incredible potential for the treatment of obesity and underlying issues with glycemic control, this study emphasizes the need to monitor and preserve skeletal muscle mass and function. The proposed data supports the value of pairing general and energetic assessment of muscle to protect muscle resilience in diabetic patients and individualize treatment regimens with adjunct treatments that can help mitigate the muscle mass, strength, and function that is lost during GLP-1 therapy.

## List of Abbreviations

$^{31}$P-MRS: phosphorus magnetic resonance spectroscopy
AMPK: AMP-activated protein kinase
BMI: body mass index
DEXA: dual energy X-ray absorptiometry
FPG: fasting plasma glucose
GLP-1: glucagon-like peptide-1
HbA1c: hemoglobin a1c
HOMA-IR: homeostatic model assessment of insulin resistance
IWQOL-lite-CT: impact of weight on quality of life-lite clinical trials version
OGTT: oral glucose tolerance test
PCr: phosphocreatine recovery
QOL: quality of life
T2DM: type 2 diabetes mellitus

**Conflicts of Interest**
The author declares that they have no conflict of interests.

**Ethics Approval and/or Participant Consent**
This study does not require Research Ethics Board (REB) approval as the work is a research protocol.

**Authors' Contributions**
BMD: primary contributions to design of study, conducted a literature search, analyzed the amassed literature, revised the manuscript critically, drafted manuscript, and gave final approval of the version to be published

**Acknowledgements**
This work would not be possible without the support and structured mentor program of the Undergraduate Research in Natural and Clinical Science and Technology (URNCST) and the mentorship and invaluable support of Mia Wilkinson.

**Funding**
This study was not funded.

**References**
[1] Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes: state-of-the-art. Mol Metab. 2021 Apr;46:101102. Available from: http://doi.org/10.1016/j.molmet.2020.101102
[2] Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022 Jan;183:109119. Available from: http://doi.org/10.1016/j.diabres.2021.109119
[3] Koivisto VA. Insulin therapy in type II diabetes. Diabetes Care. 1993 Dec;16(Suppl 3):29–39. Available from: http://doi.org/10.2337/diacare.16.3.29
[4] Harris MI. Classification and diagnostic criteria for diabetes mellitus and other categories of glucose intolerance. Prim Care. 1988 Jun;15(2):205–25. Available from: http://pubmed.ncbi.nlm.nih.gov/3290916/
[5] Thomas CC, Philipson LH. Update on diabetes classification. Med Clin North Am. 2015 Jan;99(1):1–16. Available from: https://doi.org/10.1016/j.mcna.2014.08.015
[6] Viollet B, Guigas B, Sanz García N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012 Mar;122(6):253–70. Available from: https://doi.org/10.1042/CS20110386
[7] Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care. 2009 Nov;32(Suppl 2):S151–S156. Available from: https://doi.org/10.2337/dc09S301
[8] Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metabolism. 2018 Apr;27(4):740–56. Available from: https://doi.org/10.1016/j.cmet.2018.03.001
[9] Drucker DJ. The GLP-1 journey: from discovery science to therapeutic impact. J Clin Invest. 2024 Jan 16;134(2):e175634. Available from: http://doi.org/10.1172/JCI175634
[10] Prado CM, Phillips SM, Gonzalez MC, Heymsfield SB. Muscle matters: the effects of medically induced weight loss on skeletal muscle. Lancet Diabetes Endocrinol. 2024 Nov;12(11):785–787. Available from: http://doi.org/10.1016/S2213-8587(24)00272-9
[11] Karakasis P, Patoulias DI, Fragakis N, Mantzoros CS. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: systematic review and network meta-analysis. Metabolism. 2025 Mar;164:156113. Available from: http://doi.org/10.1016/j.metabol.2024.156113
[12] Cava E, Yeat NC, Mittendorfer B. Preserving Healthy Muscle during Weight Loss. Adv Nutr. 2017 May;8(3):511–519. Available from: http://doi.org/10.3945/an.116.014506
[13] Abbatecola AM, Olivieri F, Corsonello A, Strollo F, Fumagalli A, Lattanzio F. Frailty and safety: the example of diabetes. Drug Safety. 2012 Jan;35(Suppl 1):63–71. Available from: http://doi.org/10.1007/BF03319104
[14] Marcotte-Chénard A, Oliveira B, Little JP, Candow DG. Sarcopenia and type 2 diabetes: pathophysiology and potential therapeutic lifestyle interventions. Diabetes Metab Syndr Clin Res Rev. 2023 Sep;17(9):102835. Available from: http://doi.org/10.1016/j.dsx.2023.102835
[15] Veronese N, Pizzol D, Demurtas J, Soysal P, Smith L, Sieber C, et al. Association between sarcopenia and diabetes: a systematic review and meta-analysis of observational studies. Eur Geriatr Med. 2019 Oct;10(5):685–696. Available from: http://doi.org/10.1007/s41999-019-00216-x
[16] Li GHY, Lee GKY, Au PCM, Chan M, Li HL, Cheung BMY, et al. The effect of different measurement modalities in the association of lean mass with mortality: a systematic review and meta-analysis. Osteoporos Sarcopenia. 2021 Mar;7(Suppl 1):S13–S18. Available from: http://doi.org/10.1016/j.afos.2021.02.004
[17] Yajima T, Yajima K, Takahashi H, Yasuda K. The effect of dulaglutide on body composition in type 2 diabetes mellitus patients on hemodialysis. J Diabetes Complications. 2018 Aug;32(8):759–763. Available from: http://doi.org/10.1016/j.jdiacomp.2018.05.018
[18] Volpe S, Lisco G, Fanelli M, Racaniello D, Colaianni V, Lavarra V, et al. Oral semaglutide improves body composition and preserves lean mass in patients with type 2 diabetes: a 26-week prospective real-life study. Front Endocrinol. 2023 Sep;14:1240263. Available from: http://doi.org/10.3389/fendo.2023.1240263

[19] McCrimmon RJ, Catarig AM, Frias JP, Lausvig NL, le Roux CW, Thielke D, Lingvay I, et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. Diabetologia. 2020 Jan 2;63(3):473–485. Available from: http://doi.org/10.1007/s00125-019-05065-8

[20] Harder H, Nielsen L, Thi TDT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide-1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care. 2004 Aug;27(8):1915–1921. Available from: http://doi.org/10.2337/diacare.27.8.1915

[21] Iwai S, Kaji K, Nishimura N, Kubo T, Tomooka F, Shibamoto A, et al. Glucagon-like peptide-1 receptor agonist, semaglutide attenuates chronic liver disease–induced skeletal muscle atrophy in diabetic mice. Biochim Biophys Acta Mol Basis Dis. 2023 Oct;1869(7):166770. Available from: http://doi.org/10.1016/j.bbadis.2023.166770

[22] Mastaitis JW, Gomez D, Raya JG, Li D, Min S, Stec M, et al. GDF8 and activin A blockade protects against GLP-1–induced muscle loss while enhancing fat loss in obese male mice and non-human primates. Nat Commun. 2025 May;16(1):4377. Available from: http://doi.org/10.1038/s41467-025-59485-9

[23] Rodriguez PJ, Gratzl S, Goodwin Cartwright BM, Brar R, Gluckman TJ, Stucky NL, et al. First-time prescribing of GLP-1 receptor agonists from 2018–2023: a descriptive analysis. medRxiv. 2023 Aug 22. Available from: http://doi.org/10.1101/2023.08.22.23294277

[24] Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight-loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA. 2021 Mar 23;325(14):1414–1425. Available from: http://doi.org/10.1001/jama.2021.3224

[25] Wajdlich M, Nowicki M. The impact of GLP-1 receptor agonist liraglutide on blood pressure profile, hydration, and natriuresis in diabetic patients with severely impaired kidney function. Sci Rep. 2024 Feb 29;14(1):5002. Available from: http://doi.org/10.1038/s41598-024-55724-z

[26] Bohannon RW. Grip strength: an indispensable biomarker for older adults. Clin Interv Aging. 2019 Oct 1;14:1681–1691. Available from: http://doi.org/10.2147/CIA.S194543

[27] Meyerspeer M, Boesch C, Cameron D, Dezortová M, Forbes SC, Heerschap A, et al. 31P magnetic resonance spectroscopy in skeletal muscle: experts' consensus recommendations. NMR Biomed. 2020 Feb 10;34(5):e4246. Available from: http://doi.org/10.1002/nbm.4246

[28] Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care. 2011 Feb;34(2):518–523. Available from: http://doi.org/10.2337/dc10-1546

[29] Kolotkin RL, Williams VSL, Ervin CM, Williams N, Meincke HH, Qin S, et al. Validation of a new measure of quality of life in obesity trials: Impact of Weight on Quality of Life-Lite Clinical Trials Version. Clin Obes. 2019 Apr 16(3):e12310. Available from: http://doi.org/10.1111/cob.12310

[30] Wilding JPH, Batterham RL, Calanna S, Davies M, van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021 Mar 18;384(11):989–1002. Available from: http://doi.org/10.1056/NEJMoa2032183

[31] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022 Jul 21;387(3):205–216. Available from: http://doi.org/10.1056/NEJMoa2206038

[32] Neeland IJ, Marso SP, Ayers CR, Lewis B, Oslica R, Francis W, et al. Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled clinical trial. Lancet Diabetes Endocrinol. 2021 Sep;9(9):595–605. Available from: http://doi.org/10.1016/S2213-8587(21)00179-0

[33] Bartholomew CL, Martins C, Gower B. Association between insulin sensitivity and lean mass loss during weight loss. Obesity (Silver Spring). 2024 Jun;32(6):1156–1162. Available from: http://doi.org/10.1002/oby.24022

[34] Nomura T, Kawae T, Kataoka H, Ikeda Y. Loss of lower extremity muscle strength based on diabetic polyneuropathy in older patients with type 2 diabetes: Multicenter Survey of the Isometric Lower Extremity Strength in Type 2 Diabetes Phase 2 study. J Diabetes Investig. 2021 Mar;12(3):390–397. Available from: http://doi.org/10.1111/jdi.13354

[35] Shah K, Armamento-Villareal R, Parimi N, Chode S, Sinacore DR, Hilton TN, et al. Exercise training in obese older adults prevents increase in bone turnover and attenuates decrease in hip bone mineral density induced by weight loss despite decline in bone-active hormones. J Bone Miner Res. 2011 Dec;26(12):2851–2859. Available from: http://doi.org/10.1002/jbmr.475

[36] Bajpeyi S, Pasarica M, Moro C, Conley K, Jubrias S, Sereda O, et al. Skeletal muscle mitochondrial capacity and insulin resistance in type 2 diabetes. J Clin Endocrinol Metab. 2011 Apr;96(4):1160–1168. Available from: http://doi.org/10.1210/jc.2010-1621

[37] Sreekumar R, Nair KS. Skeletal muscle mitochondrial dysfunction & diabetes. Indian J Med Res. 2007 Mar;125(3):399–410. Available from: http://ijmr.org.in/skeletal-muscle-mitochondrial-dysfunction-diabetes/

[38] Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019 Jun 29;393(10191):2636–2646. Available from: http://doi.org/10.1016/S0140-6736(19)31138-9

[39] Volpi E, Campbell WW, Dwyer JT, Johnson MA, Jensen GL, Morley JE, Wolfe RR. Is the optimal level of protein intake for older adults greater than the recommended dietary allowance? J Gerontol A Biol Sci Med Sci. 2013 Jun;68(6):677–681. Available from: http://doi.org/10.1093/gerona/gls229

[40] Martin CK, Das SK, Lindblad L, Racette SB, McCrory MA, Weiss EP, et al. Effect of calorie restriction on the free-living physical activity levels of nonobese humans: results of three randomized trials. J Appl Physiol. 2011 Apr;110(4):956–963. Available from: http://doi.org/10.1152/japplphysiol.00846.2009

[41] Heymsfield SB, Yang S, McCarthy C, Brown JB, Martin CK, Redman LM, et al. Proportion of caloric restriction-induced weight loss as skeletal muscle. Obesity (Silver Spring). 2023 Oct 8;32(1):32–40. Available from: http://doi.org/10.1002/oby.23910

[42] Viecelli C, Ewald CY. The non-modifiable factors age, gender, and genetics influence resistance exercise. Front Aging. 2022 Sep 12;3:1005848. Available from: http://doi.org/10.3389/fragi.2022.1005848

[43] Scarpelli MC, Nóbrega SR, Santanielo N, Alvarez IF, Otoboni GB, Ugrinowitsch C, et al. Muscle hypertrophy response is affected by previous resistance training volume in trained individuals. J Strength Cond Res. 2022 Apr;36(4):1153–1157. Available from: http://doi.org/10.1519/JSC.0000000000003558

[44] Wilding JPH, Batterham RL, Davies M, van Gaal LF, Kandler K, Konakli K, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. Diabetes Obes Metab. 2022 Aug;24(8):1553–1564. Available from: http://doi.org/10.1111/dom.14725

[45] Budini B, Luo S, Tam M, Stead I, Lee A, Akrami A, et al. Trajectory of weight regain after cessation of GLP-1 receptor agonists: a systematic review and nonlinear meta-regression. medRxiv. 2025 Jun 9. Available from: http://doi.org/10.1101/2025.06.09.25328726

[46] Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. Adv Nutr. 2017 May 15;8(3):511–519. Available from: http://doi.org/10.3945/an.116.014506

**Article Information**
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Mia Wilkinson, Selva Lakshman Murali
Article Dates: Received Jul 30 25; Accepted Nov 01 25; Published Dec 03 25

**Citation**
Please cite this article as follows:
Mei-Dan B. Research protocol: Effects of GLP-1 therapy on skeletal muscle health across stages of type 2 diabetes. URNCST Journal. 2025 Dec 03: 9(11). https://urncst.com/index.php/urncst/article/view/957
DOI Link: https://doi.org/10.26685/urncst.957