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Increasing Skeletal Muscle Mass and Strength During Incretin-Based Weight Loss

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Abstract

Incretin-based therapies produce robust weight loss in obesity and type 2 diabetes mellitus (T2DM), but a substantial proportion of weight lost is lean body mass (LBM), raising concern about sarcopenia and functional decline. Hypogonadal men with obesity and T2DM are particularly predisposed to muscle loss. Whether concurrent anabolic therapy can preserve skeletal muscle mass (SMM) during incretin-mediated weight loss remains unknown. This retrospective case series reports on the results of 93 hypogonadal men (BMI ≥30 kg/m², testosterone <400 ng/dL) with (N=45) or without (N=48) T2DM were treated for obesity with or without T2DM at a single outpatient clinic. All patients received weekly tirzepatide, testosterone cypionate, and lifestyle coaching emphasizing resistance exercise and high-protein nutrition. Body composition was measured by multi-frequency segmental bioelectrical impedance analysis, and grip strength by dynamometry, at baseline and 3, 6, and 12 months. Laboratory measures included hemoglobin A1c (HbA1c), high sensitivity-CRP (hs-CRP), and LDL cholesterol. Patient-reported outcomes were assessed using the PROMIS Global Health 10. Over 12 months, body mass decreased by 20.9-22.6 kg (18-20%) and fat mass declined 16.6-17.1 kg (38-40%). LBM decreased 4.0-6.1 kg, considerably less than reported with incretin monotherapy. SMM increased by 1.6-3.7 kg (4-12%), and grip strength improved 5.7-7.1 kg (18-21%). In diabetic patients, HbA1c fell from 10.1% to 5.8%. LDL cholesterol decreased by 20% and hs-CRP declined 43-53%. PROMIS physical and mental health scores improved significantly by 13-16% in both groups. In hypogonadal men with obesity, a comprehensive program combining tirzepatide, testosterone, resistance exercise, and lifestyle coaching produced substantial fat loss and cardiometabolic improvements while simultaneously increasing SMM and grip strength over 12 months. These findings suggest that concurrent anabolic therapy and resistance exercise may attenuate the lean mass loss typically associated with incretin therapies, though prospective randomized trials are needed to confirm these results.

Keywords: body composition; hypogonadism; resistance training; skeletal muscle mass; testosterone; tirzepatide

1. Introduction

Obesity and type 2 diabetes mellitus (T2DM) frequently co-occur with male hypogonadism, forming a self-reinforcing triad of metabolic dysfunction. Approximately one-third to one-half of men with obesity or T2DM have low testosterone levels, a prevalence that rises when both conditions coexist [1]. The resulting hypogonadism promotes further fat accumulation, insulin resistance, and loss of lean mass in a perpetuating cycle that worsens cardiometabolic risk [1]. Tirzepatide, a dual glucagon-like peptide-1 (GLP-1) receptor and glucose-dependent insulinotropic polypeptide (GIP) agonist, has demonstrated robust weight reduction of 15-21% and marked improvements in glycemic control and lipid profiles in large clinical trials [2,3]. However, approximately 25% of the weight lost with tirzepatide is lean body mass (LBM) rather than fat mass (FM), raising concern about sarcopenia and functional decline, particularly in populations already predisposed to muscle loss such as hypogonadal men [4]. Testosterone replacement therapy increases LBM, FM, and attenuates diet-

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induced muscle loss in men with obesity and hypogonadism [5], yet no study has examined whether concurrent testosterone therapy can preserve LBM or skeletal muscle mass (SMM) during incretin-mediated weight loss. This retrospective case series describes 12-month outcomes in hypogonadal men with obesity, with and without T2DM, treated with tirzepatide plus testosterone cypionate and supported by weekly lifestyle coaching.

2. Materials and Methods

2.1. Eligibility

This series included ninety-three hypogonadal men treated for obesity with (N=45, mean age 48.3 years, range 40.3 to 58.8 years) or without (N=48, mean age 49.3 years, range 40.5 to 59.8 years) T2DM at a single outpatient clinic comprised this retrospective case series. The study adhered to the Declaration of Helsinki. The case series used de-identified data generated during routine clinical care, and formal IRB approval was not necessary. Patients were included if they were between the ages of 40-60 years, had a BMI ≥ 30 kg/m², and a serum testosterone < 400 ng/dL along with a positive Androgen Deficiency in the Aging Male (ADAM) screening questionnaire [6], indicating symptomatic hypogonadism [7,8]. Patients were excluded from this series if they had prostate-specific antigen (PSA) ≥4.0 ng/mL, polycythemia, active infection, malignancy, advanced cardiovascular disease, metal implants, or were planning to conceive during the treatment period.

2.2. Clinical Laboratory Testing, Grip Strength, and Body Composition

Hemoglobin A1c (HbA1c), serum testosterone, high-sensitivity C-reactive protein (hs-CRP), a complete blood count, comprehensive metabolic panel, lipid panel, and PSA were measured at all time points. After initiating treatment with testosterone labs were drawn as close to the treatment trough value as possible, and testosterone labs >36 hours from the 7-day trough were excluded from analysis. Patients were classified as non-diabetic (hemoglobin A1c < 6.5%) or diabetic (hemoglobin A1c ≥ 6.5% cohort). A Jamar digital dynamometer (Patterson Medical, Warrenville, IL) measured grip strength in the dominant hand. An InBody 270 system (InBody, Cerritos, CA) measured body composition.

2.3. Medication

Patients were prescribed tirzepatide (Mounjaro or Zepbound) starting at a dose of 2.5 mg weekly. For obese non-diabetic patients, the dose was increased as tolerated, contingent on weight loss plateauing at the current dose. For T2DM patients, the dose was increased based on both weight loss progress and glycemic control. Dose adjustments were made at follow-up or coaching visits. All patients who were in the cohort for the full year had reached a dose of 12.5 mg or 15 mg of tirzepatide. Of the 45 T2DM patients, 36 were taking metformin or a sulfonylurea with inadequate glycemic control (HbA1c > 7.0%), and their antidiabetic medication was discontinued before initiating tirzepatide. Non-diabetic patients were not taking any weight-loss medication. Testosterone cypionate was delivered intramuscularly starting at 100 mg weekly, with the dose adjusted based on symptom resolution and tolerance.

2.4. Outcomes

Patients completed the PROMIS Global Health 10 to assess general physical and mental health outcomes [9]. Raw scores were converted to T-scores for analysis.

2.5. Coaching

To improve treatment adherence, interactive weekly coaching sessions were conducted in-person or over SMS messaging. The topics of coaching sessions are listed in Table 1. Patients received adherence reminders and weekly education covering topics including physical activity, diet, obesity,

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glycemic control, metabolism, hypogonadism, cardiovascular disease, fitness, and healthy aging. Patients were instructed to consume 150–200 g of protein daily and to perform more than 150 minutes of weekly exercise, with 60–70% consisting of resistance training. For simplicity and convivence, coaching around protein intake focused on absolute amounts instead of g protein per kg body weight.

Table 1. Topics for coaching curriculum. Educational topics covered in weekly coaching sessions delivered in-person or via SMS messaging.

Topic	Number of Sessions
Exercise	**16**
Exercise selection, progression, and program design	4
Mobility, flexibility, and injury prevention	2
Optimizing athletic performance	3
Recovery	2
Science of aerobic fitness	2
Science of muscle hypertrophy	3
Nutrition	**14**
Caloric deficits	2
General macros	2
Hydration	1
Meal prep and planning	1
Optimizing blood sugar	1
Pre- and post-exercise nutrition	2
Protein prioritization	4
Supplements	1
Pharmacology	**3**
How GLP-1 medications work	1
Other obesity and diabetes medications	1
Testosterone	1
Healthy aging	**6**
Cardiovascular health	3
Gut health	1
Maintaining cognitive fitness	1
Osteoporosis	1
Lifestyle	**13**
Alcohol	1
Blood pressure	1
Blood sugar and continuous glucose monitors	1
Erectile function, libido, and sexual performance	2
Stress and anxiety	3
Sleep	3
Work-life balance	2

2.6. Physical Activity

Self-reported average physical activity was quantified on an ordinal scale: 1, no moderate or vigorous activity; 2, <150 minutes of moderate or <75 minutes of vigorous weekly activity; 3, 150-300 minutes of moderate or 75-150 minutes of vigorous weekly activity; 4, >300 minutes of moderate or >150 minutes of vigorous weekly activity.

2.7. Statistics

Continuous outcomes were analyzed with a linear mixed effects model (α=0.05) that included glycemic group, time, and the group by time interaction as fixed effects and a random intercept for each patient, estimated by restricted maximum likelihood. For each outcome, we compared non-diabetic and diabetic patients at each time point, and also compared all pairs of time points within each glycemic (non-diabetic or diabetic) group. Multiple comparisons were controlled using the Holm-Sidak method. Physical activity scores (α=0.05) were compared with Mann-Whitney U tests

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between groups and Wilcoxon signed-rank tests within groups, with Holm-Sidak corrections. Analyses were performed in Python 3.12 with statsmodels 0.14 and SciPy 1.17. Values presented are estimated marginal mean ± 95% confidence interval.

3. Results

Ninety-three men were included, N=48 without T2DM (-T2DM) and N=45 with T2DM (+T2DM). By 12 months N=40 non-diabetic and N=36 diabetic patients remained in follow-up.

3.1. Body Mass and Composition

Both groups experienced considerable changes in body composition over 12 months (Figure 1). Body mass decreased 22.6 kg (20%) in non-diabetics and 20.9 kg (18%) in diabetics, with parallel reductions in BMI, transitioning from class II obesity to class I obesity and overweight (Figure 1A-B). FM decreased 16.6 kg (40%) in non-diabetics and 17.1 kg (38%) in diabetics, body fat percentage fell approximately 9 percentage points in both groups, with body fat percentage and adiposity indices declining in concert (Figure 1C-G). LBM decreased 6.1 kg in non-diabetics (8%) and 4.0 kg in diabetics (5%) (Figure 1F-G). SMM increased, by 1.6 kg in non-diabetics (4%) and 3.7 kg in diabetics (12%) (Figure 1H-I). Grip strength improved 7.1 kg in non-diabetics (21%) and 5.7 kg in diabetics (18%) (Figure 1J).

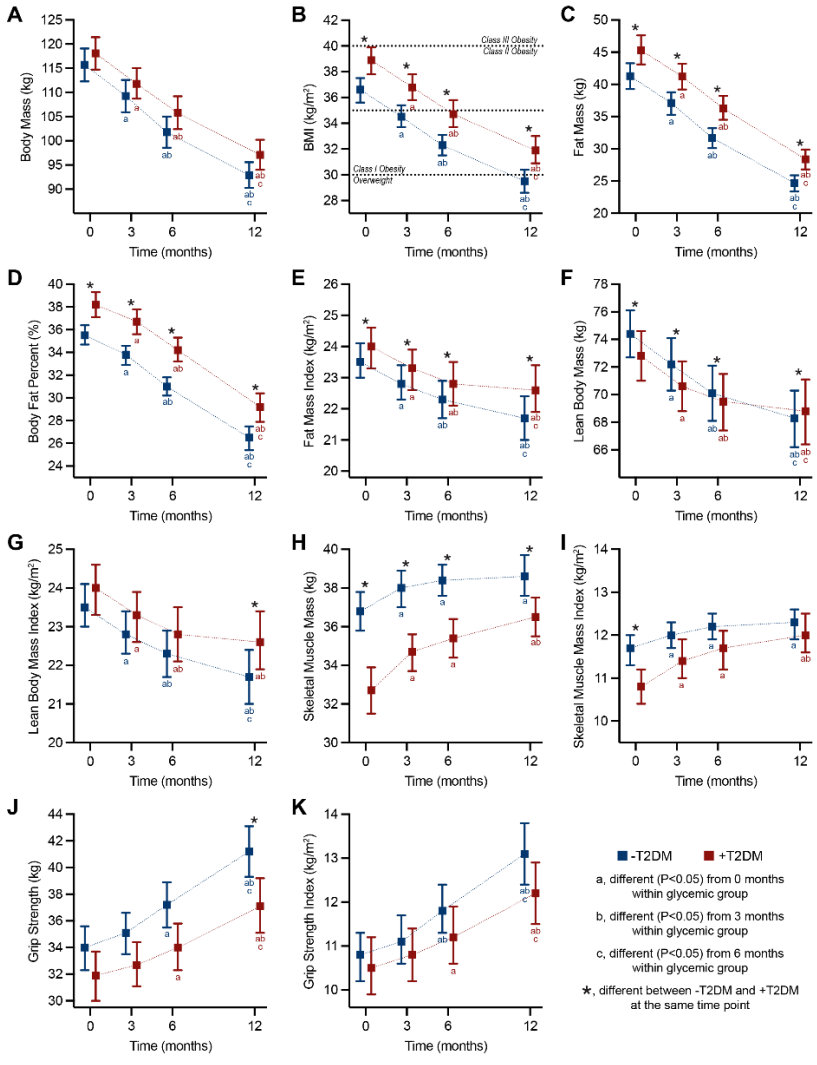

Figure 1. Body mass, body composition, and grip strength over 12 months of tirzepatide treatment in obese men without (-T2DM) and with (+T2DM) type 2 diabetes mellitus. (A) Body mass, (B) body mass index, (C) fat mass,

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(D) body fat percentage, (E) fat mass index, (F) lean body mass, (G) lean body mass index, (H) skeletal muscle mass, (I) skeletal muscle mass index, (J) grip strength, (K) grip strength index. Values are means with 95% confidence intervals from a linear mixed effects model. Post-hoc sorting: a, different from 0 months within the same glycemic (-T2DM or +T2DM) group; b, different from 3 months; c, different from 6 months; *, different between -T2DM and +T2DM at the same time point. At baseline N=48 (-T2DM) and N=45 (+T2DM), declining over follow-up to N=40 (-T2DM) and N=36 (+T2DM) at 12 months.

3.2. Laboratory Measures

HbA1c fell in diabetics by 43%, from 10.1% to 5.8%, converging with non-diabetics by 12 months (Figure 2A). Testosterone rose considerably, with treatment trough levels approximately doubling from baseline (Figure 2B). For hs-CRP, levels fell below the high-risk threshold in both groups, by 43% in non-diabetics and 53% in diabetics (Figure 2C). LDL cholesterol decreased about 20% in both groups, entering the near-optimal range (Figure 2D).

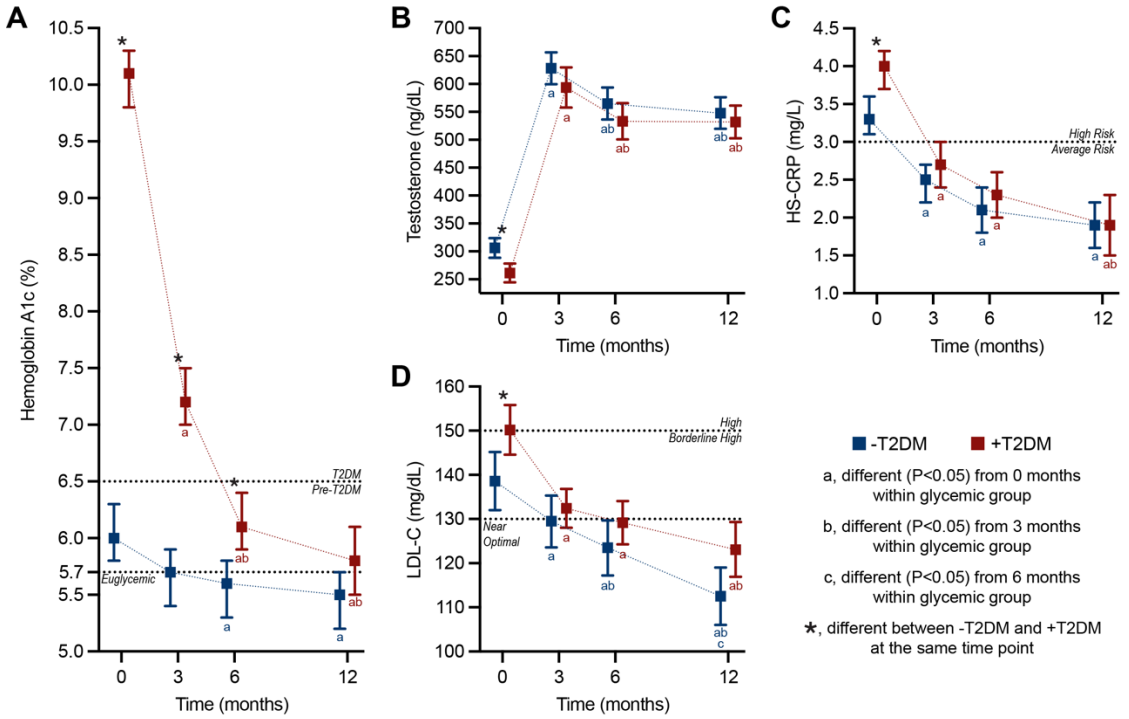

Figure 2. Glycemic, hormonal, inflammatory, and lipid measures over 12 months of tirzepatide treatment in obese men without (-T2DM) and with (+T2DM) type 2 diabetes mellitus. (A) Hemoglobin A1c, (B) testosterone, (C) high-sensitivity C-reactive protein (HS-CRP), (D) LDL cholesterol. Reference lines mark clinical thresholds. Values are means with 95% confidence intervals from a linear mixed effects model. Post-hoc sorting: a, different from 0 months within the same glycemic (-T2DM or +T2DM) group; b, different from 3 months; c, different from 6 months; *, different between -T2DM and +T2DM at the same time point. At baseline N=48 (-T2DM) and N=45 (+T2DM), declining over follow-up to N=40 (-T2DM) and N=36 (+T2DM) at 12 months. For testosterone, samples sizes ranged from N=22 to N=48.

3.3. Patient-Reported Outcomes and Physical Activity

PROMIS physical and mental component scores improved in both groups over 12 months, by 16% and 14% in non-diabetics and 13% and 15% in diabetics, with no between-group differences at any time point (Figure 3). Self-reported physical activity shifted toward higher categories in both groups, with over 75% of patients engaging in regular physical activity and up to 63% engaging in over 150 minutes of regular exercise weekly (Figure 4).

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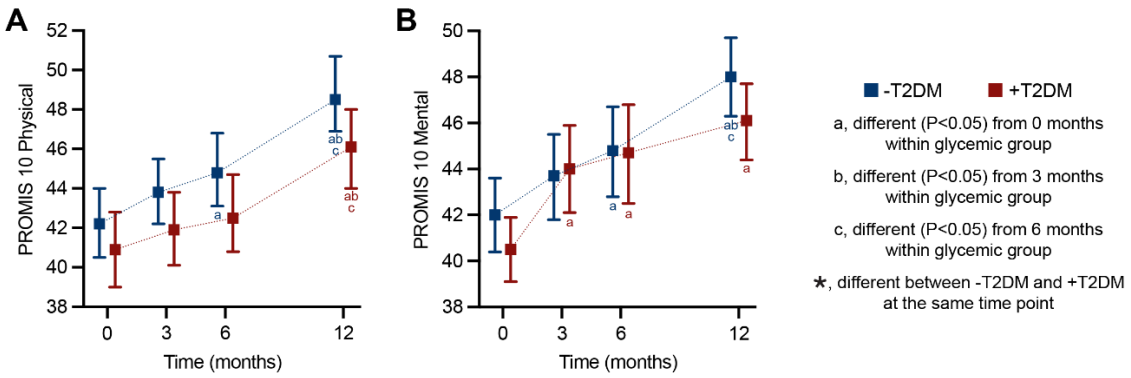

Figure 3. Patient-reported outcome measures over 12 months of tirzepatide treatment in obese men without (-T2DM) and with (+T2DM) type 2 diabetes mellitus. (A) PROMIS Global Health 10 physical component summary score and (B) PROMIS Global Health 10 mental component summary score. Values are means with 95% confidence intervals from a linear mixed effects model. Post-hoc sorting: a, different from 0 months within the same glycemic (-T2DM or +T2DM) group; b, different from 3 months; c, different from 6 months; *, different between -T2DM and +T2DM at the same time point. At baseline N=48 (-T2DM) and N=45 (+T2DM), declining over follow-up to N=40 (-T2DM) and N=36 (+T2DM) at 12 months.

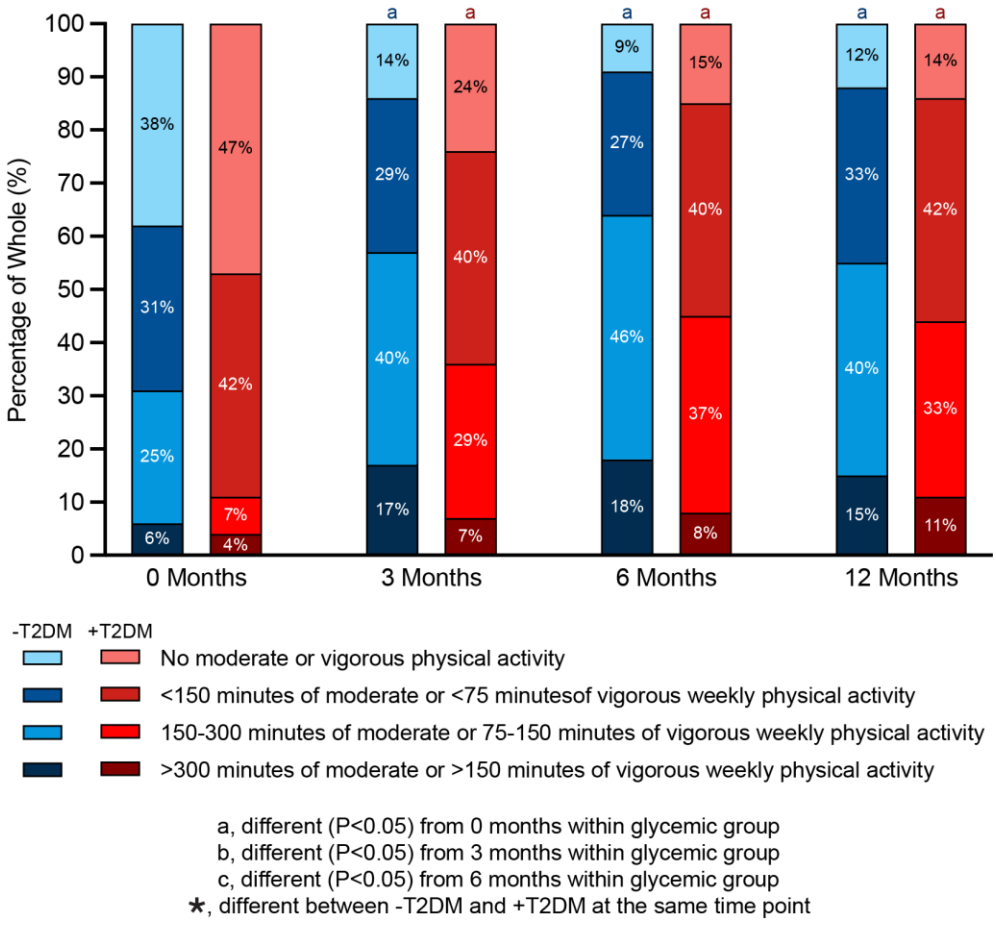

Figure 4. Self-reported physical activity over 12 months of tirzepatide treatment in obese men without (-T2DM) and with (+T2DM) type 2 diabetes mellitus. Stacked bars show the percentage of patients in each activity category at each time point. Differences between groups were tested with Mann-Whitney U tests and differences within groups with Wilcoxon signed-rank tests, with Holm-Sidak corrections. Post-hoc sorting: a, different from 0 months; b, different from 3 months; c, different from 6 months; *, different between -T2DM and +T2DM at the same time point. At baseline N=48 (-T2DM) and N=45 (+T2DM), declining over follow-up to N=40 (-T2DM) and N=36 (+T2DM) at 12 months.

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4. Discussion

Incretin-based therapies have transformed the treatment of obesity and type 2 diabetes, with considerable reductions in FM along with marked improvements in glycemic control, lipid profiles, and inflammation, while reducing the burden of cardiovascular, kidney, and liver disease [10]. However, a consistent limitation of all weight-loss interventions, including incretin therapies, is the loss of SMM [11]. Preserving or increasing muscle tissue during obesity treatment is important because increased SMM is associated with better insulin sensitivity and glycemic control, lower cardiometabolic risk, improved physical function, reduced frailty risk, and greater long-term weight maintenance after fat loss [11]. Men with hypogonadism are at greater risk of developing obesity and T2DM, and having disproportionately greater impacts of these diseases on their health [1]. To address this gap, we developed a structured, biologically informed clinical treatment program for obesity and T2DM integrating four complementary strategies: (i) tirzepatide for robust FM reduction and glycemic control; (ii) testosterone to promote muscle hypertrophy and oppose atrophy; (iii) resistance exercise emphasizing progressive overload to further potentiate muscle protein synthesis; and (iv) weekly lifestyle coaching centered on high-protein nutrition (150-200 g/day) and behavioral adherence. This multimodal approach was designed to shift the composition of weight loss towards FM while preserving or increasing SMM. In the present cohort, we achieved clinically relevant reductions in FM, glycemic load, LDL, and inflammation while improving SMM, strength, and quality of life.

4.1. Body Composition and Strength Changes

An important consideration when interpreting body composition changes during weight loss is the distinction between LBM and SMM. LBM encompasses not only skeletal muscle (45-60%) but also organs, total body water, glycogen-associated water, connective tissue, and other nonfat soft tissues (40-55%) [12]. This distinction is clinically consequential during weight loss, as reductions in water, glycogen, organ mass, and adipocyte stroma that accompany a shrinking body habitus are captured within the lean mass compartment [12]. Some healthy reduction in LBM is expected during weight loss, as organs, connective tissue, and fluid volumes contract proportionally with overall body size [13]. When measuring changes in body composition during weight loss, many studies use dual x-ray absorptiometry (DXA), which has high accuracy in measuring LBM and FM, but cannot distinguish SMM from LBM [14]. MRI and CT are the most accurate in vivo methods for quantifying SMM [15] but have practical limitations in a clinical setting. The present study measured LBM and SMM using a multi-frequency segmental bioelectrical impedance analysis (BIA) device. BIA shows strong agreement with reference standards, with SMM correlating well with MRI ($r = 0.97$) and BF correlating well with DXA ($r = 0.89$) [16,17].

The magnitude of total weight reduction observed here is broadly consistent with the 15-21% reductions reported in large clinical trials [2,3]. However, the body composition profile diverges markedly from those trials. In obese non-diabetic men, tirzepatide reduced DXA-measured lean mass by 10% alongside a 36% reduction in fat mass [4]. For overweight to obese diabetic subjects treated with tirzepatide, MRI analysis demonstrated a 5.5% reduction in thigh muscle volume which was proportional to changes in body weight, suggesting that tirzepatide does not cause muscle loss beyond what would be expected from weight reduction alone [18]. The differential effects of incretin therapeutics on LBM versus SMM have been further supported by preclinical studies. In obese male mice treated with semaglutide, body mass decreased by 9%, with 10% reductions in both FM and LBM [19,20]. Semaglutide reduced the wet mass of solid organs by 33%, with an 8% reduction in wet mass of muscles, but no change in muscle fiber cross-sectional area, fiber type distribution, or maximum isometric force was observed [19]. Consistent with these observations, in obese patients treated with semaglutide for 6 months, there was no change in grip strength despite a 5% reduction in SMM [21].

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Outside of incretin therapy, there is robust evidence that supports the role of resistance exercise and testosterone in favorably modifying body composition during weight loss. At the biochemical level, resistance exercise activates mechanotransduction through the mTORC1 pathway, whereby mechanical loading stimulates phosphorylation of p70S6K and 4E-BP1 to increase ribosomal biogenesis and muscle protein synthesis, while simultaneously suppressing muscle protein breakdown through Akt-mediated phosphorylation and nuclear exclusion of FoxO transcription factors, which prevents upregulation of the E3 ubiquitin ligases MuRF1 and atrogin-1 [22,23]. Testosterone binds to the androgen receptor (AR) to activate similar pathways as resistance exercise, while transcriptionally upregulating multiple genes involved in myogenesis and muscle contractility and blocking expression of atrophy-related genes [24–26].

A meta-analysis of 114 trials found that resistance training during caloric restriction was the most effective strategy for reducing fat mass while maintaining lean mass, whereas caloric restriction without resistance training resulted in significant lean mass loss [27]. Resistance training was also the only exercise modality associated with fat-free mass gains during caloric restriction, while aerobic exercise and no exercise groups both lost lean mass [28]. In a controlled trial of men undergoing a 40% energy deficit with concurrent resistance and high-intensity interval training, a high-protein diet produced a net gain of 1.2 kg in lean body mass alongside a 4.8 kg reduction in fat mass over 4 weeks, demonstrating that body recomposition is achievable during caloric restriction with appropriate protein intake and exercise stimulus [29]. Testosterone therapy provides complementary benefits. In the absence of concurrent exercise or dietary intervention, hypogonadal men treated with 125 mg/week of testosterone enanthate for 52 weeks, LBM increased by 7% (4.0 kg) and BF decreased by 10% (3.9 kg), while grip strength improved by 11.3% (0.8 kg) and upper and lower body muscle 1-repetition maximum strength increased by 8-14% (5.3-12.9 kg) [30]. In another study, hypogonadal men receiving 125 mg/week of testosterone enanthate gained 5.5% (3.5 kg) LBM, with 5-7% increases (150 to 200 N) in leg-press strength [31]. Meta-analyses of 48 studies assessing the impact of exercise alone, testosterone alone, or combined therapy found that exercise alone improved both LBM and muscle strength, testosterone alone also improved LBM and strength, and their combination produced greater gains in LBM and strength than either intervention in isolation, although the effects were diminished with advanced age [32,33]. In a 56-week RCT that combined testosterone with a very low energy diet (640 kcal/day transitioning to 1350 kcal/day after 10 weeks) and moderate-intensity exercise in obese hypogonadal men, compared with placebo injection testosterone produced a 45% greater reduction in fat mass (-9.6 kg testosterone vs -6.5 kg placebo) and attenuated LBM loss by 85% (-0.6 kg testosterone vs -4.0 kg placebo) [34]. This indicated that the weight loss in testosterone-treated men was almost exclusively due to loss of body fat while total body weight loss did not differ between groups [34]. Collectively, these data demonstrate that resistance exercise preserves muscle function and attenuates lean mass loss, testosterone shifts the composition of weight loss toward fat, and the combination may produce additive benefits.

4.2. Hemoglobin A1c Changes

Across the SURPASS phase 3 program, tirzepatide reduced HbA1c by 1.9-2.6 percentage points from baseline values of 7.9-8.5%, with 31-52% of participants reaching euglycemia at 40-52 weeks [35,36]. In the current study, we observed a 4.3 percentage point reduction in HbA1c, from a mean of 10.1% to 5.8%, with 42% of subjects reaching euglycemia. The higher baseline HbA1c likely reflects differences in patient selection and clinical setting relative to trial sites. In the current study we had 12 patients who were newly diagnosed with T2DM and 36 who had inadequately managed T2DM in primary care, while clinical trials are typically conducted at specialized centers where clinicians are highly motivated to optimize glycemic management. The HbA1c reductions observed here likely reflect several factors affecting insulin signaling and skeletal muscle glucose uptake.

Patients with obesity and T2DM often have an accumulation of intramuscular adipose tissue (IMAT) that can contribute to insulin insensitivity and elevated HbA1c. IMAT accumulates in obesity and T2DM through aberrant adipogenic differentiation of fibro-adipogenic progenitors, which

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impair skeletal muscle insulin signaling by releasing ceramide and diacylglycerol (DAG) into the local muscle microenvironment [37–39]. Ceramide and DAG activate PKCθ and NFκB pathways that block PI3K/Akt signaling downstream of the insulin receptor [37–39]. Tirzepatide can reduce IMAT through GLP-1R-mediated AMPK activation in skeletal muscle to promote beta-oxidation of accumulated fatty acids and apoptosis of fibro-adipogenic cells, while the GIPR component reduces the systemic lipid overflow that drives ectopic muscle fat deposition by improving postprandial triglyceride clearance into dedicated adipose depots and enhancing fasted-state lipolysis via hormone-sensitive lipase activation [40,41]. Consistent with this finding, the SURPASS-3 MRI substudy identified a 5.1% reduction in IMAT in patients treated with tirzepatide [18].

Patients in the current study were encouraged to engage in regular resistance exercise, which can activate GLUT4 translocation through a contraction-mediated pathway that is entirely distinct from insulin signaling, relying instead on calcium/calmodulin-dependent protein kinase II (CaMKII), AMPK, and downstream Rab-GTPase/SNARE machinery, resulting in increased glucose disposal and reduced HbA1c [42,43]. A meta-analysis of 43 studies identified that resistance exercise results in a 0.6 percentage point reduction in HbA1c in patients with T2DM [44]. Testosterone interacts with insulin signaling through both non-genomic and genomic pathways. Upon binding to the AR, testosterone activates PI3K through non-genomic AR interactions, engaging the canonical insulin signaling pathway to promote GLUT4 translocation, intramyocellular glucose uptake, and glycogen synthesis via GSK3β inhibition [45,46]. At the genomic level, activated AR upregulates the expression of several genes involved in insulin signaling, including insulin receptor β subunit, IRS-1, Akt, and GLUT4 [47]. Testosterone therefore enhances insulin sensitivity both by amplifying PI3K signaling downstream of the insulin receptor, and by increasing levels of proteins involved in insulin sensing and signal transduction in muscle cells [45–47]. Consistent with the biochemical effects of testosterone, a meta-analysis of 18 RCTs found that testosterone reduced HbA1c by 0.7-0.8 percentage points in men with T2DM [48]. The considerable improvement in HbA1c in this study is therefore likely due to the pharmacological actions of tirzepatide and testosterone, along with the physiological effects of resistance exercise.

4.3. Inflammation and LDL Changes

CRP declined 43-53% in both groups, falling below the average-risk cardiovascular threshold. CRP is transcribed in hepatocytes primarily through IL-6–driven JAK–STAT3 signaling, with TNF-α and IL-1β amplifying this response via NF-κB co-activation of the CRP promoter [49]. Each component of the treatment program targets this inflammatory cascade through distinct mechanisms. Tirzepatide suppresses the TLR4/NF-κB/NLRP3 inflammasome pathway and promotes anti-inflammatory M2 macrophage polarization in adipose tissue, with meta-analyses showing a 33% reduction in hs-CRP partly independent of weight loss [50–53]. Testosterone reinforces this effect by stabilizing IκBα to prevent NF-κB nuclear translocation and reducing macrophage TLR4 expression, consistent with observational data demonstrating an inverse association between testosterone and CRP in men with obesity [54–56]. Resistance exercise further attenuates systemic inflammation by stimulating muscle-derived myokine release that triggers anti-inflammatory IL-10 and IL-1ra production while downregulating NF-κB activity [57]. These convergent anti-inflammatory mechanisms likely contributed to the magnitude of CRP reduction observed across both cohorts, and the transition from the high to average risk category is clinically meaningful given the well-established association between elevated CRP and increased risk of cardiovascular events, metabolic disease progression, and all-cause mortality [58].

LDL cholesterol decreased approximately 20% in both cohorts, transitioning from borderline-high to near-optimal levels. In the SURPASS trials, tirzepatide reduced LDL cholesterol by 5-8% in patients with T2DM, with the largest reductions seen in the high-cardiovascular-risk SURPASS-4 population [36,59]. The LDL reductions observed in the present cohort substantially exceed those reported with tirzepatide monotherapy, suggesting additive contributions from the other program components. At the molecular level, testosterone suppresses hepatic PCSK9 through AR-mediated

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signaling, thereby increasing hepatic LDL receptor density and enhancing LDL breakdown [60]. Resistance exercise reduces PCSK9 and SREBP-2/LDLR expression in hepatocytes, providing a further modest but consistent LDL-lowering effect of 6-13 mg/dL [61–63]. The approximate 20% LDL reduction observed here is clinically meaningful, as both cohorts transitioned from the borderline-high category at baseline to the near-optimal range [64] by 12 months.

4.4. Health Outcomes and Coaching

The improvements in PROMIS physical and mental health scores and the shift toward higher self-reported physical activity categories are clinically meaningful and likely reflect the combined effects of weight loss, improved body composition, testosterone-mediated improvements in energy and mood, and the weekly coaching intervention [9,65,66]. Weekly outreach, delivered primarily over SMS with some in-person sessions, provided a low-burden coaching touchpoint that reinforced medication adherence, nutrition goals, resistance training, physical activity, self-monitoring, medication dose adjustments, and early identification and management of side effects or behavioral barriers. This ongoing contact may have contributed to the observed improvements in obesity and diabetes outcomes, as text message-based behavioral interventions have been shown to produce modest but significant improvements in weight loss, BMI, physical activity, and glycemic control, including reductions in HbA1c among patients with diabetes [67,68].

4.5. Limitations

Several limitations warrant consideration. The retrospective, single-center design without a control group precludes causal inference, and the independent contributions of tirzepatide, testosterone, and lifestyle coaching cannot be disentangled. Body composition was assessed by BIA rather than DXA or MRI, which may be less precise for tracking lean mass changes. BIA is most accurate for detecting changes at the group level [69], which is the level of analysis employed in the present study. Additionally, BIA estimates are sensitive to hydration status, and the large shifts in total body water that accompany rapid weight loss and testosterone-induced fluid retention could influence the lean mass estimates in opposing directions, potentially underestimating fat loss while overestimating lean mass gains [70]. Despite these limitations, the use of a single device across all patients and time points in the present study ensured internal consistency. The observed improvements in grip strength further support the interpretation that SMM gains reflect genuine hypertrophy [71]. The cohort was exclusively male and ranged from 40 to 60 years of age, limiting generalizability to women and other age groups. Attrition over 12 months (17% in non-diabetics, 20% in diabetics) may introduce survivorship bias. We did not track diet or physical activity using accelerometry or detailed logs, limiting insight into more detailed dietary or activity parameters.

5. Conclusions

This retrospective case series demonstrates that a comprehensive treatment program combining tirzepatide, testosterone cypionate, resistance exercise, and high-protein lifestyle coaching produced substantial fat mass reductions and improvements in glycemic control, LDL cholesterol, and systemic inflammation in men with obesity and hypogonadism, with and without T2DM, while simultaneously increasing skeletal muscle mass and grip strength over 12 months. Unlike prior incretin trials, in which 25% or more of weight lost was lean mass, the present cohort gained skeletal muscle and strength while losing fat, suggesting that concurrent anabolic therapy and structured lifestyle intervention can shift the composition of weight loss away from lean mass and toward fat. These findings were consistent across both non-diabetic and diabetic subgroups, with diabetic patients achieving a 4.3 percentage point reduction in HbA1c to near-euglycemic levels. The absence of a control group and the retrospective design preclude causal attribution to any single intervention, and prospective randomized trials are needed to isolate the independent and combined contributions of each program component. Nonetheless, these results provide a clinical rationale for integrating

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anabolic pharmacotherapy with incretin-based weight loss strategies in hypogonadal men and support the feasibility of preserving musculoskeletal health during aggressive obesity treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

ADAM	Androgen Deficiency in the Aging Male
Akt	Protein kinase B
AMPK	AMP-activated protein kinase
AR	Androgen receptor
BF	Body fat
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CaMKII	Calcium/calmodulin-dependent protein kinase II
CRP	C-reactive protein
CT	Computed tomography
DAG	Diacylglycerol
DXA	Dual-energy X-ray absorptiometry
FM	Fat mass
FoxO	Forkhead box O
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GLUT4	Glucose transporter type 4
GSK3β	Glycogen synthase kinase 3 beta
HbA1c	Hemoglobin A1c
hs-CRP	High-sensitivity C-reactive protein
IκBα	Inhibitor of kappa B alpha
IL-1β	Interleukin-1 beta
IL-1ra	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IL-10	Interleukin-10
IMAT	Intramuscular adipose tissue
IRS-1	Insulin receptor substrate 1
JAK	Janus kinase
LBM	Lean body mass
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
MRI	Magnetic resonance imaging
mTORC1	Mechanistic target of rapamycin complex 1
MuRF1	Muscle RING-finger protein 1
NF-κB	Nuclear factor kappa B
NLRP3	NLR family pyrin domain-containing 3

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PCSK9	Proprotein convertase subtilisin/kexin type 9
PI3K	Phosphoinositide 3-kinase
PKCθ	Protein kinase C theta
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Prostate-specific antigen
RCT	Randomized controlled trial
SMM	Skeletal muscle mass
SMS	Short message service
SNARE	Soluble N-ethylmaleimide-sensitive factor attachment protein receptor
SREBP-2	Sterol regulatory element-binding protein 2
STAT3	Signal transducer and activator of transcription 3
T2DM	Type 2 diabetes mellitus
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor alpha
+T2DM	With type 2 diabetes mellitus
-T2DM	Without type 2 diabetes mellitus

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