https://doi.org/10.31925/farmacia.2026.4.8 **ORIGINAL ARTICLE**

METABOLIC, BODY COMPOSITION, AND INFLAMMATION OUTCOMES FOLLOWING SECOND-LINE ANTIDIABETIC THERAPIES IN TYPE 2 DIABETES MELLITUS: A ONE-YEAR PROSPECTIVE COHORT STUDY

IOANA BUJDEI-TEBEICĂ [1]*, ANCA MIHAELA PANTEA-STOIAN [1,2], DOINA ANDRADA MIHAI [1,2], SIMONA DIANA ȘTEFAN [2], CRISTIAN SERAFINCEANU [1,2]

[1]Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy "Carol Davila", 030167 Bucharest, Romania
[2]National Institute of Diabetes, Nutrition and Metabolic Diseases "Prof. N.C. Paulescu", 030167 Bucharest, Romania

**corresponding author: ioana.paunica@drd.umfcd.ro*

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Abstract

Type 2 diabetes mellitus (T2DM) with obesity requires a comprehensive assessment spanning glycemic control, adiposity, muscle function, renal function, and low-grade inflammation. This prospective cohort study in Bucharest, Romania, evaluated one-year associations between metformin-based antidiabetic regimens and glycemic, body composition, functional, renal, and high-sensitivity C-reactive protein (hs-CRP) outcomes. Of 291 adults assessed, 166 completed 12-month follow-up without treatment change and were classified into six groups: metformin (n = 46), sulfonylurea (n = 10), DPP-4 inhibitor (n = 17), SGLT2 inhibitor (n = 25), GLP-1 receptor agonist (GLP-1 RA; n = 23), and insulin (n = 45). Outcomes were analyzed using baseline-adjusted regression with robust HC3 standard errors. Compared with metformin, GLP-1 RA therapy was associated with lower 12-month HbA1c (β = -0.745%), body weight (β = -5.246 kg), fat mass percentage (β = -2.731 points), and ln(hs-CRP) (β = -0.459), while handgrip strength and eGFR remained stable. GLP-1 RA showed the most favorable multidimensional profile, with no adverse muscle or renal effects. These findings support the integration of body composition and inflammatory markers into T2DM assessment, though the associations are observational rather than causal.

Rezumat

Diabetul zaharat de tip 2 (DZ2) asociat cu obezitate necesită o evaluare complexă, care să includă controlul glicemic, adipozitatea, funcția musculară, stabilitatea renală și inflamația de grad scăzut. Acest studiu de cohortă prospectiv, desfășurat în București, România, a evaluat asocierile pe parcursul unui an dintre regimurile antidiabetice bazate pe metformină și rezultatele glicemice, de compoziție corporală, funcționale, renale și cele privind proteina C reactivă înalt sensibilă (hs-CRP). Dintre cei 291 de adulți evaluați, 166 au finalizat perioada de urmărire de 12 luni fără modificarea tratamentului și au fost clasificați în șase grupuri: metformină (n = 46), sulfoniluree (n = 10), inhibitor de DPP-4 (n = 17), inhibitor de SGLT2 (n = 25), agonist al receptorului GLP-1 (GLP-1 RA; n = 23) și insulină (n = 45). Rezultatele au fost analizate prin regresie ajustată la valorile inițiale, cu erori standard robuste HC3. Comparativ cu metformina, terapia cu GLP-1 RA a fost asociată cu valori mai scăzute ale HbA1c (β = -0,745%), greutății corporale (β = -5,246 kg), procentului de masă grasă (β = -2,731 puncte) și ln(hs-CRP) (β = -0,459), la 12 luni, în timp ce forța de prehensiune palmară și RFGe au rămas stabile. GLP-1 RA a prezentat cel mai favorabil profil multidimensional, fără efecte adverse musculare sau renale. Aceste rezultate susțin integrarea markerilor de compoziție corporală și inflamatori în evaluarea DZ2, deși asocierile sunt de natură observațională, nu cauzală.

Keywords: type 2 diabetes mellitus, body composition, fat mass; handgrip strength, low-grade inflammation

Introduction

Type 2 diabetes mellitus (T2DM) is frequently accompanied by obesity and adverse changes in body composition, including increased visceral fat and reduced muscle quality, factors that contribute to insulin resistance, cardiovascular risk, and functional decline (1). While guidelines increasingly advocate individualized treatment strategies, most clinical trials emphasize glycemic endpoints (*e.g.* HbA1c) without systematically capturing body composition or physical function (2, 3).

Central and Eastern Europe have experienced substantial increases in obesity-related T2DM in the past two decades. Regional epidemiological data suggest an age-standardized diabetes prevalence increase of approximately 30 - 40% since the early 2000s, compared with 15-20% in Western Europe; this trend is documented across EU member states, with prevalence, incidence, and expenditure all rising progressively over recent decades (4).

Despite the growing burden of obesity-driven T2DM in Eastern Europe, patients from this region remain underrepresented in major randomized controlled

trials (RCTs) of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Consequently, real-world data capturing metabolic and functional outcomes in routine clinical practice are essential for complementing RCT evidence and informing treatment strategies tailored to populations at higher cardiometabolic risk (5). This is particularly important because real-world studies consistently show GLP-1 RAs discontinuation rates of 20 - 50% within the first year and use of lower doses than studied in trials, resulting in attenuated outcomes compared with the controlled trial setting (6).

Beyond the classical triad of hyperglycemia, insulin resistance, and progressive beta-cell dysfunction, T2DM is now recognized as a state of chronic, low-grade systemic inflammation. This inflammatory substrate is not merely a downstream consequence of metabolic dysregulation but an active contributor to disease progression, vascular injury, and the amplification of insulin resistance itself (7, 8). Inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) have been shown to predict the development of T2DM and its complications, suggesting that low-grade inflammation already increases before diagnosis and may persist despite pharmacological glycemic control (7). At the molecular level, excess adiposity drives macrophage infiltration into adipose tissue, triggering the release of tumor necrosis factor-alpha (TNF-α) and IL-6, which in turn stimulate hepatic CRP synthesis and impair insulin receptor signaling through the NF-κB and JNK pathways (9). The result is a self-reinforcing cycle in which metabolic dysfunction and inflammation are mutually sustaining.

Second-line antidiabetic agents such as SGLT2 inhibitors (SGLT2i) and GLP-1 RAs are known to promote weight loss. Yet, their comparative effects on fat mass and muscle strength in routine care remain poorly characterized. Moreover, evidence suggests that treatment response may vary by sex, *e.g.* women bear a greater burden of obesity at diagnosis, show higher relative cardiovascular risk than men with T2DM, and are less likely to receive guideline-recommended therapy (10). Understanding the broader physiological impact of these therapies, including on fat distribution and strength, may help optimize clinical decisions beyond glycemic metrics alone.

To address this, we conducted a prospective cohort study in an urban tertiary care center to evaluate the relationship between antidiabetic treatment class and metabolic outcomes, including HbA1c, body composition, and muscle strength, after 12 months of therapy. We also explored sex-specific differences in treatment response. We hypothesized that GLP-1 RAs would be associated with greater reductions in HbA1c and adiposity without negatively affecting muscle strength, and that these effects would be more pronounced in men.

Materials and Methods

Study Design, Setting, and Participants

This prospective observational cohort study was conducted at the National Institute of Diabetes, Nutrition and Metabolic Diseases Prof. N. Paulescu, which is a tertiary referral center in Bucharest, Romania. Baseline assessments were performed during routine outpatient visits between June and December 2024, and assessments at 12 months of follow-up were completed from June to December 2025.

Adults with confirmed T2DM receiving metformin monotherapy or metformin-based therapy with initiation or continuation of a pre-specified second-line antidiabetic class were evaluated. Patients were considered eligible when baseline (clinical, anthropometric, functional, and laboratory) data were available and if the therapeutic regimen was assigned to one of the pre-specified analytic groups. Exclusion criteria included cases of complex or unclassifiable treatments, continuous triple therapy outside the analytical framework, patients with severe anemia and/or hypertriglyceridemia, duplicate records, missing baseline data, incomplete key variables, treatment change during follow-up, withdrawal from the study, inability to follow up during the study, or absence of assessment at 12 months.

Of the 291 screened adults, 202 met eligibility criteria. Eighty-nine patients evaluated were not included due to failure to meet eligibility criteria (n = 30), missing baseline data (n = 30), or duplicate records (n = 29). Of the 202 eligible patients, 166 continued the same antidiabetic regimen for 12 months, completing the follow-up period and thus providing the key variables required for the primary analysis. 36 eligible patients were not included due to missing follow-up data (n = 8), treatment change (n = 7), loss to follow-up (n = 7), withdrawal (n = 7), or incomplete key data (n = 7). Therefore, the final analysis was a full cohort of 166 patients. Patients not included or excluded from the primary analysis were recorded only to control for study flow and selection bias. The flow of the study population is shown in Figure 1.

All participants provided written informed consent. The study protocol was approved by the Ethics Committee of the Carol Davila University of Medicine and Pharmacy, Bucharest (approval number 1514, dated 03.06.2022), and the study was conducted in accordance with the Declaration of Helsinki.

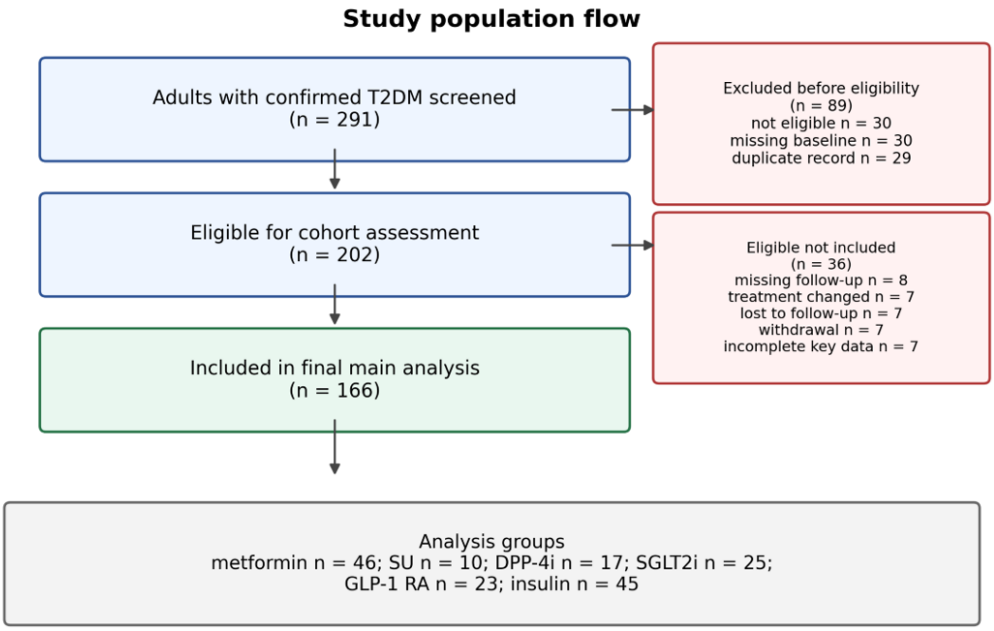

Figure 1.
Study participant flow diagram showing screening, eligibility assessment, exclusions, final analysis set, and treatment-group distribution

Treatment groups and exposure definition

Treatment allocation was not randomized, in accordance with routine clinical decision-making. The main exposure variable was the antidiabetic regimen maintained throughout the 12-month observation period. Patients either received metformin alone, classified as monotherapy, or received metformin as background therapy in combination with a second-line agent. Patients were classified in the statistical analysis into six groups: metformin monotherapy (n = 46), metformin plus sulfonylurea (SU; n = 10), metformin plus dipeptidyl peptidase-4 inhibitor (DPP-4i; n = 17), metformin plus sodium-glucose cotransporter-2 inhibitor (SGLT2i; n = 25), metformin plus glucagon-like peptide-1 receptor agonist (GLP-1 RA; n = 23), and metformin plus insulin (n = 45). Because metformin was continued as background therapy in every non-monotherapy group, all treatment arms were metformin-backgrounded, with the metformin monotherapy group serving as the common reference; the term "metformin-based" in the title reflects this shared metformin backbone across all arms.

Sulfonylureas and DPP-4 inhibitors were retained as separate analytical groups (rather than pooled) because these drug classes differ in mechanism of action, expected effects on weight, risk of hypoglycemia, and potential inflammatory profiles. Therefore, results for the SU and DPP-4 inhibitor groups should be interpreted with caution due to small sample sizes.

All patients received routine nutritional counseling in accordance with local standards of diabetes care. Lifestyle variables, including physical activity level, resistance training, estimated protein intake, and adherence indicators, were recorded when available and used descriptively or as potential sources of residual confounding.

Clinical, anthropometric, functional, and laboratory assessments

Baseline variables included age, sex, duration of diabetes, smoking, menopausal status (where applicable), hypertension, cardiovascular disease, chronic kidney disease, dyslipidemia, obesity class, concomitant use of statins, ACE inhibitors, or angiotensin receptor blockers, recent infection, and use of anti-inflammatory drugs or glucocorticoids.

Anthropometric assessment included weight, height, body mass index (BMI), waist circumference, hip circumference, and waist-to-height ratio. Body composition was assessed using the Fresenius body composition monitor (Fresenius Medical Care Body Composition Monitor), with patients in the supine position (11). Percentage fat mass, fat mass in kilograms, lean mass, and skeletal muscle mass were recorded when available. Muscle strength was measured using a Saehan hydraulic handgrip dynamometer; the best of three maximal voluntary contractions in the dominant hand was used for analysis (12). Handgrip measurements were performed with the participant seated, the shoulder adducted, the elbow flexed at a 90-degree angle, and the wrist in a neutral position, with a 15-30-second rest interval between the three maximal contractions.

Glycemic and biochemical parameters included HbA1c, fasting blood glucose, insulin, C-peptide, HOMA-IR, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, and

triglycerides), serum creatinine, estimated glomerular filtration rate (eGFR), urea, urinary albumin, and albumin-to-creatinine ratio. HbA1c was measured by high-performance liquid chromatography. Other biochemical parameters were measured using standardized automated methods in the institution's certified laboratory.

Inflammatory status was assessed using erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and white blood cell count. hs-CRP was measured using a dedicated, highly sensitive assay (being therefore considered a valid marker of low-grade systemic inflammation). Because the distributions of CRP and hs-CRP were right-skewed, logarithmic transformations were used for adjusted inflammatory models.

Outcomes

The primary endpoint was HbA1c at 12 months, adjusted for baseline HbA1c and prespecified clinical covariates. The single primary contrast, specified *a priori*, was GLP-1 RA versus metformin monotherapy for 12-month HbA1c; all other comparisons were pre-specified secondary analyses. Continuous secondary endpoints included body weight, BMI, waist circumference, percent fat mass, fat mass in kilograms, lean mass, skeletal muscle mass, handgrip strength, eGFR, ln(hs-CRP), and ESR at 12 months. For each longitudinal endpoint, the absolute change from baseline to 12 months was also calculated.

Predefined binary endpoints included achieving an HbA1c level of < 7% at 12 months, a reduction in HbA1c of at least 0.5 percentage points, a reduction in HbA1c of at least 1.0 percentage points, a weight loss of at least 5% from baseline, and a combined response defined as both a reduction in HbA1c of at least 0.5 percentage points and a weight loss of at least 5%.

Statistical analysis

The primary statistical analysis included 166 patients who completed the 12-month follow-up period without treatment changes. Patients excluded from the primary analysis were included in participant flow and in comparisons between included and eligible but excluded patients. Missing values were not estimated; analyses were performed using only complete cases for each specified outcome.

Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were summarized as counts and percentages. Baseline continuous variables were compared across treatment groups using the Kruskal-Wallis test, and categorical variables were compared using the chi-square test, with low expected cell counts flagged for cautious interpretation (13). Unadjusted within-group changes from baseline to 12 months were assessed using paired Wilcoxon signed-rank tests, and between-group differences in change were assessed using Kruskal-Wallis tests (13, 14).

Adjusted continuous outcomes were analyzed using ordinary least-squares regression with HC3 robust standard errors. Metformin monotherapy was used as the reference group. All adjusted models included the treatment group and the baseline value of the corresponding outcome. Additional covariates were selected *a priori* according to outcome type. For the HbA1c outcome, the model adjusted for baseline HbA1c, age, sex, diabetes duration, and baseline BMI. Weight and BMI models adjusted for baseline value, age, sex, diabetes duration, and baseline HbA1c. Fat mass models adjusted for baseline fat mass, age, sex, diabetes duration, and baseline BMI. The handgrip model adjusted for baseline handgrip strength, age, sex, baseline BMI, and baseline fat mass percentage. The eGFR model adjusted for baseline eGFR, age, sex, diabetes duration, and baseline BMI. The inflammatory model for ln(hs-CRP) adjusted for the baseline log-transformed inflammatory marker, age, sex, diabetes duration, baseline BMI, statin use, and recent infection.

Binary endpoints were analyzed using logistic or binomial generalized linear models with HC3 robust standard errors, where estimable. The adjusted models for glycemic target achievement and HbA1c response included treatment group, baseline HbA1c, age, sex, diabetes duration, and baseline BMI. The weight-loss model included treatment group, baseline weight, age, sex, diabetes duration, and baseline HbA1c. The combined-response model included treatment group, baseline HbA1c, baseline weight, age, sex, diabetes duration, and baseline BMI. Associations among baseline variables and among 12-month changes (Section 3.8) were quantified using Spearman rank correlation coefficients to verify the internal consistency of physiologically related measures and to contextualize the relationships among adiposity, muscle function, and inflammatory change. These correlation analyses were descriptive and not adjusted for multiplicity.

Sex-specific treatment heterogeneity was explored using treatment-by-sex interaction models. Because treatment groups were unbalanced, particularly the SU and DPP-4i groups, subgroup and interaction results were considered exploratory. Multiplicity was addressed using Benjamini-Hochberg false discovery rate (FDR) q-values for overall delta tests, adjusted OLS treatment contrasts, and logistic treatment contrasts (15). Statistical tests were two-tailed, with a nominal $p < 0.05$ considered statistically significant, and FDR q-values were reported to support interpretation of multiple comparisons. The FDR families (overall delta tests, adjusted OLS treatment contrasts, and logistic treatment contrasts) were prespecified, and the GLP-1 RA versus metformin

HbA1c contrast was designated *a priori* as the single primary comparison, interpreted separately from the secondary battery.

Statistical analyses were performed using Python 3.13 with Pandas for data management, NumPy for numerical computation, SciPy for non-parametric and categorical tests, and StatsModels for regression modeling (16, 17). Figures were generated based on the results of the statistical analysis. Figure 2 was produced in Python using Matplotlib; the participant-flow diagram (Figure 1) was prepared using Python 3.10.

Results and Discussion

Study population and baseline characteristics

Of the 291 adults with type 2 diabetes evaluated, 202 were eligible, and 166 were retained in the final analysis set. The 166 patients eligible for analysis were allocated to six treatment groups: metformin monotherapy (n = 46), add-on sulfonylurea therapy (SU, n = 10), add-on DPP-4 inhibitor therapy (DPP-4i, n = 17), add-on SGLT2 inhibitor therapy (SGLT2i, n = 25), add-on GLP-1 receptor agonist therapy (GLP-1 RA, n = 23), and add-on insulin therapy (n = 45). The 36 eligible patients who were not retained in the primary analysis and the 89 ineligible patients were used only for flow and selection bias checks.

Overall, the cohort had long-standing type 2 diabetes mellitus (T2DM) associated with obesity. The mean age was 59.7 ± 13.0 years; 99 patients (59.6%) were female; the mean duration of diabetes was 13.7 ± 7.7 years; the mean HbA1c at baseline was 8.9 ± 1.0%; and the mean BMI was 36.3 ± 4.4 kg/m². Baseline body composition and inflammatory burden were consistent with an obese cardiometabolic phenotype, with a mean percent fat mass of 40.4 ± 6.1% and a mean hs-CRP of 5.4 ± 3.0 mg/L. Most baseline variables did not differ significantly between treatment groups. Modest differences were observed between groups in waist-to-height ratio and LDL-cholesterol, while HbA1c showed only a nonsignificant trend toward higher baseline values in the insulin group. These imbalances support the use of baseline-adjusted models rather than unadjusted comparisons. Baseline characteristics of the final analysis cohort are summarized in Table I.

Table I

Baseline characteristics of the final analysis cohort

Variable	Overall	Median [IQR]	Overall group p-value
Age, years	59.7 ± 13.0	59.0 [49.0; 70.8]	0.138
Diabetes duration, years	13.7 ± 7.7	12.9 [7.4; 18.9]	0.658
HbA1c, %	8.9 ± 1.0	9.0 [8.2; 9.7]	0.095
Weight, kg	102.6 ± 17.8	102.5 [90.1; 115.2]	0.772
BMI, kg/m²	36.3 ± 4.4	36.2 [32.8; 39.6]	0.273
Waist circumference, cm	126.6 ± 8.3	127.0 [121.0; 132.0]	0.831
Fat mass, %	40.4 ± 6.1	39.9 [35.9; 44.4]	0.202
Handgrip strength, kg	30.8 ± 10.1	29.6 [22.9; 37.2]	0.291
eGFR, mL/min/1.73 m²	100.6 ± 11.2	101.0 [92.0; 109.0]	0.639
hs-CRP, mg/L	5.4 ± 3.0	5.0 [3.2; 6.8]	0.646
ESR, mm/h	29.1 ± 10.7	28.0 [19.2; 38.8]	0.302
Female sex	99 (59.6%)		0.699
Hypertension	111 (66.9%)		0.573
Dyslipidemia	110 (66.3%)		0.495
Statin use	104 (62.7%)		0.716

Legend: Continuous variables are shown as mean ± SD and median [IQR]. Categorical variables are shown as n (%). Overall group comparisons used the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

Glycemic outcomes

HbA1c decreased significantly in all treatment groups over 12 months, but the magnitude of improvement differed substantially between groups. The unadjusted mean change in HbA1c ranged from -0.5 ± 0.2 percentage points with metformin to -1.2 ± 0.2 percentage points with GLP-1 RA therapy and -1.0 ± 0.3 percentage points with insulin. The between-group comparison of HbA1c change was significant after FDR adjustment ($q < 0.001$). Unadjusted 12-month changes from baseline for all key outcomes are summarized in Figure 2.

In baseline-adjusted OLS models with robust HC3 standard errors, the treatment group remained strongly associated with HbA1c at 12 months (overall $p < 0.001$). Compared with metformin, GLP-1 RA therapy had the largest adjusted difference in HbA1c ($\beta = -0.745$ percentage points, 95% CI -0.856 to -0.634; $p < 0.001$; FDR $q < 0.001$). SGLT2i and insulin were also associated with lower adjusted HbA1c at 12 months compared with metformin (SGLT2i: $\beta = -0.364$, 95% CI -0.489 to -0.240; $p < 0.001$; insulin: $\beta = -0.575$, 95% CI -0.685 to -0.464; $p < 0.001$). DPP-4i reached nominal significance

versus metformin, but this contrast did not remain significant after FDR adjustment ($p = 0.028$; $q = 0.069$). Adjusted treatment contrasts versus metformin for the key continuous outcomes are presented in Table II.

Analyses of responders provided complementary clinical information. An HbA1c value < 7% at 12 months was achieved by 26.1% of patients treated with GLP-1 RA, compared with 6.5% in the metformin group, 10.0% in the SU group, 17.6% in the DPP-4i group, 12.0% in the SGLT2i group, and 4.4% in the insulin group. Reductions of at least 0.5 percentage points were common in the SGLT2i, GLP-1 RA, and insulin groups, while a reduction of at least 1.0 percentage point was most common in the GLP-1 RA group (91.3%). Analyses of responders should be interpreted primarily descriptively, as rare events produced unstable logistic estimates. Responder rates by treatment group are shown in Table III.

Body weight, BMI, waist circumference, and body composition

Weight trajectories differed significantly between treatment groups. GLP-1 RA therapy produced the greatest unadjusted weight reduction (-6.6 ± 1.2 kg), followed by SGLT2i (-3.3 ± 1.2 kg) and metformin (-1.2 ± 1.3 kg). In contrast, weight increased in the SU group (+1.6 ± 1.2 kg) and the insulin group (+1.9 ± 1.3 kg), while DPP-4i was essentially weight neutral (-0.4 ± 1.6 kg). The difference between groups in weight change remained significant after FDR adjustment ($q < 0.001$).

Adjusted models confirmed this hierarchy. Compared with metformin, GLP-1 RA therapy was associated with substantially lower weight at 12 months after adjustment for baseline weight and clinical covariates ($\beta = -5.246$ kg, 95% CI -5.921 to -4.572; $p < 0.001$; FDR $q < 0.001$). SGLT2i was also associated with lower adjusted weight compared with metformin ($\beta = -2.050$ kg, 95% CI -2.692 to -1.407; $p < 0.001$), whereas SU and insulin were associated with higher adjusted weight at 12 months. Similar patterns were observed for BMI and waist circumference, with GLP-1 RA showing the most favorable adjusted profile.

Fat mass percentage showed a parallel pattern. Unadjusted fat mass percentage decreased most strongly with GLP-1 RAs (-3.4 ± 1.1 percentage points) and SGLT2i (-1.6 ± 0.7 percentage points), changed only modestly with metformin (-0.7 ± 0.9 percentage points) or DPP-4i (-0.4 ± 1.0 percentage points), and increased slightly with insulin (+0.6 ± 1.0 percentage points). In adjusted models, GLP-1 RA remained the most favorable contrast to metformin in terms of fat mass percentage ($\beta = -2.731$ percentage points, 95% CI -3.266 to -2.195; $p < 0.001$; FDR $q < 0.001$). Fat mass in kilograms showed the same directionality, with an adjusted contrast of GLP-1 RAs of -4.689 kg versus metformin (95% CI -5.462 to -3.916; $p < 0.001$).

Lean mass and skeletal muscle mass were relatively stable. Lean mass at 12 months did not differ significantly by treatment group in the adjusted model (overall $p = 0.124$). The GLP-1 RA contrast for skeletal muscle mass was nominally smaller than that of metformin ($\beta = -0.386$ kg, 95% CI -0.766 to -0.005; $p = 0.047$), but this did not remain significant after FDR adjustment ($q = 0.104$). Consequently, the weight loss observed with GLP-1 RA was predominantly driven by reduced adiposity rather than a clear decrease in functional muscle strength.

Muscle strength and renal function

Handgrip strength did not show a clinically unfavorable trajectory in either treatment group. The unadjusted changes were small and generally positive, ranging from +0.5 ± 1.6 kg in the insulin group to +1.1 ± 1.5 kg in the SU group. The between-group comparison of change in handgrip strength was not significant (FDR $q = 0.797$), and the adjusted treatment model also showed no significant overall treatment effect (overall $p = 0.792$). The adjusted contrast of GLP-1 RA versus metformin was nearly null ($\beta = +0.273$ kg, 95% CI -0.579 to +1.124; $p = 0.530$; FDR $q = 0.731$).

Renal function remained stable in all groups. Mean changes in eGFR were small, ranging from -1.0 ± 2.7 mL/min/1.73 m² in the GLP-1 RA group to +0.7 ± 3.0 mL/min/1.73 m² in the insulin group, with no significant difference between groups after FDR adjustment. The adjusted model for eGFR at 12 months did not show a significant overall treatment effect ($p = 0.262$), and none of the treatment-versus-metformin comparisons were statistically significant.

Inflammatory markers

High-sensitivity CRP was analyzed as a measured inflammatory endpoint. Unadjusted hs-CRP decreased in several groups, with the greatest absolute reduction in the GLP-1 RA group (-1.2 ± 0.9 mg/L), followed by SGLT2i (-1.0 ± 1.2 mg/L), metformin (-0.6 ± 1.2 mg/L), DPP-4i (-0.6 ± 0.9 mg/L), SU (-0.5 ± 1.3 mg/L), and insulin (-0.3 ± 1.2 mg/L). The difference between groups in change in hs-CRP was significant after FDR adjustment ($q = 0.036$). The cohort's mean baseline hs-CRP (5.4 ± 3.0 mg/L) lay above the conventional< 3 mg/L range used to define chronic low-grade inflammation and at the threshold of clinically significant inflammation; consequently, some individual baseline values may have reflected acute-phase activity rather than chronic low-grade inflammation, and results should be interpreted with this in mind.

Because hs-CRP is right-skewed, the adjusted inflammatory model used ln(hs-CRP) at 12 months as the dependent variable. Treatment group was significantly associated with ln(hs-CRP) at 12 months (overall $p = 0.015$). Compared with metformin,

GLP-1 RA therapy was associated with a lower adjusted ln(hs-CRP) (β = -0.459, 95% CI -0.828 to -0.090; p = 0.015; FDR q = 0.038), corresponding to an approximately 36.8% lower hs-CRP level after adjustment for covariates. The SGLT2i contrast was nominally significant (β = -0.214; p = 0.042), but did not remain significant after FDR adjustment (q = 0.097). Insulin, SU, and DPP-4i did not differ significantly from metformin in the adjusted ln(hs-CRP) model. ESR decreased modestly in several groups, but between-group differences and adjusted treatment contrasts were not significant.

Figure 2. Unadjusted 12-month change from baseline in key outcomes by treatment group

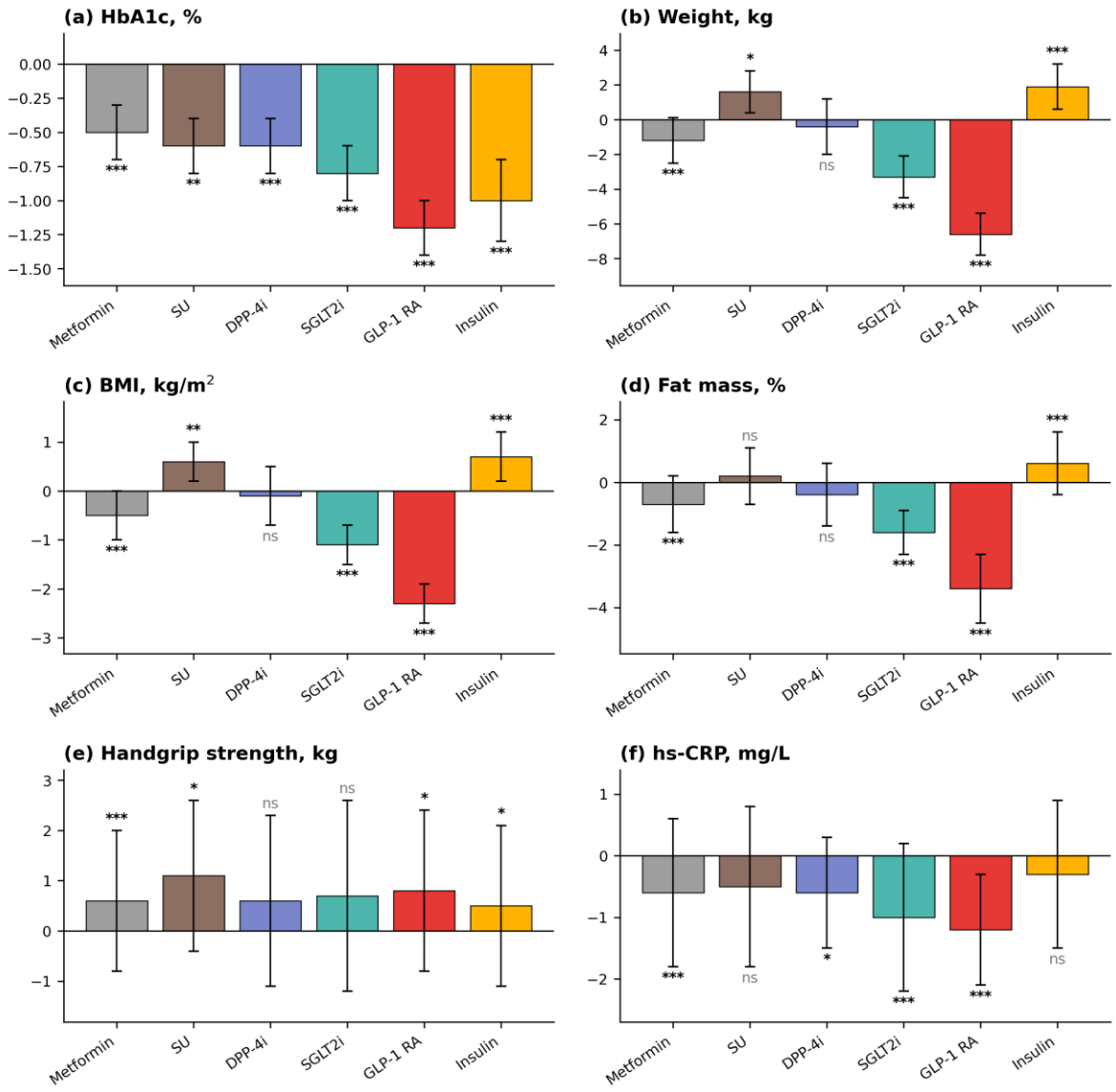

Figure 2.

Unadjusted 12-month change from baseline in key outcomes by treatment group, shown as separate panels: (a) HbA1c, (b) body weight, (c) BMI, (d) percent fat mass, (e) handgrip strength, and (f) hs-CRP. Bars show the mean change with SD error bars. Within-group paired Wilcoxon significance is indicated as ***p < 0.001, **p < 0.01, *p < 0.05, ns = not significant. Between-group differences in change were significant after FDR adjustment for HbA1c, weight, BMI, fat mass percentage, waist circumference, and hs-CRP, but not for handgrip strength or eGFR

Table II

Adjusted treatment contrasts versus metformin for key continuous outcomes

Outcome	Contrast	Adjusted β	95% CI	p-value	FDR q-value
HbA1c	SU *vs.* MF	-0.148	-0.310 to 0.015	0.075	0.150
HbA1c	DPP-4i *vs.* MF	-0.161	-0.305 to -0.018	0.028	0.069
HbA1c	SGLT2i *vs.* MF	-0.364	-0.489 to -0.240	< 0.001	< 0.001
HbA1c	GLP-1 RA *vs.* MF	-0.745	-0.856 to -0.634	< 0.001	< 0.001
HbA1c	insulin *vs.* MF	-0.575	-0.685 to -0.464	< 0.001	< 0.001
Weight	SU *vs.* MF	2.871	2.013 to 3.730	< 0.001	< 0.001
Weight	DPP-4i *vs.* MF	0.877	-0.022 to 1.776	0.056	0.121
Weight	SGLT2i *vs.* MF	-2.050	-2.692 to -1.407	< 0.001	< 0.001
Weight	GLP-1 RA *vs.* MF	-5.246	-5.921 to -4.572	< 0.001	< 0.001
Weight	insulin *vs.* MF	3.248	2.660 to 3.837	< 0.001	< 0.001
Fat mass %	SU *vs.* MF	0.943	0.234 to 1.653	0.009	0.024
Fat mass %	DPP-4i *vs.* MF	0.206	-0.408 to 0.820	0.510	0.716
Fat mass %	SGLT2i *vs.* MF	-0.901	-1.317 to -0.484	< 0.001	< 0.001
Fat mass %	GLP-1 RA *vs.* MF	-2.731	-3.266 to -2.195	< 0.001	< 0.001
Fat mass %	insulin *vs.* MF	1.318	0.908 to 1.729	< 0.001	< 0.001
Handgrip	SU *vs.* MF	0.658	-0.416 to 1.732	0.230	0.368
Handgrip	DPP-4i *vs.* MF	0.279	-0.683 to 1.241	0.570	0.754
Handgrip	SGLT2i *vs.* MF	0.128	-0.689 to 0.944	0.759	0.880
Handgrip	GLP-1 RA *vs.* MF	0.273	-0.579 to 1.124	0.530	0.731
Handgrip	insulin *vs.* MF	-0.091	-0.734 to 0.553	0.783	0.882
eGFR	SU *vs.* MF	-0.138	-2.394 to 2.117	0.904	0.934
eGFR	DPP-4i *vs.* MF	-0.042	-1.923 to 1.840	0.965	0.965
eGFR	SGLT2i *vs.* MF	-0.092	-1.692 to 1.508	0.910	0.934
eGFR	GLP-1 RA *vs.* MF	-1.259	-2.838 to 0.319	0.118	0.214
eGFR	insulin *vs.* MF	0.819	-0.490 to 2.128	0.220	0.360
ln(hs-CRP)	SU *vs.* MF	0.035	-0.238 to 0.309	0.799	0.886
ln(hs-CRP)	DPP-4i *vs.* MF	-0.048	-0.309 to 0.213	0.720	0.860
ln(hs-CRP)	SGLT2i *vs.* MF	-0.214	-0.422 to -0.007	0.042	0.097
ln(hs-CRP)	GLP-1 RA *vs.* MF	-0.459	-0.828 to -0.090	0.015	0.038
ln(hs-CRP)	insulin *vs.* MF	0.024	-0.145 to 0.193	0.781	0.882

OLS models used HC3-robust standard errors, with metformin as the reference group. Each model was adjusted for the baseline value of the corresponding outcome and prespecified clinical covariates. For hs-CRP, the model used ln(hs-CRP).

Table III

Responder rates by treatment group

Group	HbA1c < 7% at 12m	HbA1c reduction ≥ 0.5%	HbA1c reduction ≥ 1.0%	Weight loss ≥ 5%	Combined response
Metformin	3/46 (6.5%)	22/46 (47.8%)	0/46 (0.0%)	0/46 (0.0%)	0/46 (0.0%)
SU	1/10 (10.0%)	8/10 (80.0%)	1/10 (10.0%)	0/10 (0.0%)	0/10 (0.0%)
DPP-4i	3/17 (17.6%)	14/17 (82.4%)	1/17 (5.9%)	0/17 (0.0%)	0/17 (0.0%)
SGLT2i	3/25 (12.0%)	25/25 (100.0%)	9/25 (36.0%)	1/25 (4.0%)	1/25 (4.0%)
GLP-1 RA	6/23 (26.1%)	23/23 (100.0%)	21/23 (91.3%)	20/23 (87.0%)	20/23 (87.0%)
Insulin	2/45 (4.4%)	45/45 (100.0%)	31/45 (68.9%)	0/45 (0.0%)	0/45 (0.0%)

Combined response was defined as an HbA1c reduction of > 0.5 percentage points plus weight loss of > 5%. Logistic models for sparse endpoints produced very wide confidence intervals; therefore, responder findings should be interpreted primarily as descriptive and hypothesis-generating.

Responder and combined-response analyses

The combined clinical endpoint of HbA1c reduction ≥ 0.5 percentage points and weight loss ≥ 5% was observed almost exclusively in the GLP-1 RA group. Twenty of 23 GLP-1 RA-treated patients (87.0%) achieved this combined response, compared with 1 of 25 SGLT2i-treated patients (4.0%) and none of the patients treated with metformin, SU, DPP-4i, or insulin. The same distribution was observed for weight loss ≥ 5%, indicating that the combined responder endpoint was driven primarily by the weight-loss component among patients who also achieved glycemic improvement.

Sex-specific analyses

Descriptive analyses stratified by sex showed numerically similar reductions in HbA1c among women and men treated with GLP-1 RA (women: -1.3 ± 0.2; men: -1.2 ± 0.2). Weight loss and fat mass reduction were also substantial in both sexes in the GLP-1 RA group (weight: women -6.6 ± 0.9, men -6.7 ± 1.4; percent fat mass: women -3.3 ± 1.0, men -3.5 ± 1.2). However, formal testing of treatment-sex interaction did not identify statistically significant interaction

effects for HbA1c (p = 0.342), weight (p = 0.09), fat mass percentage (p = 0.277), handgrip strength (p = 0.146), or ln(hs-CRP) (p = 0.882). Therefore, sex-specific differences should be considered exploratory rather than confirmatory.

Correlation analysis and internal consistency

Correlation analyses supported the dataset's internal consistency and helped contextualize the functional and inflammatory findings. Baseline triglycerides were almost perfectly correlated with VLDL cholesterol (Spearman r = 1.000), total cholesterol was strongly correlated with LDL-C (r = 0.870), and urinary albumin was strongly correlated with albumin-to-creatinine ratio (r = 0.954), as expected for physiologically related or partially derived variables. Baseline waist circumference was moderately correlated with waist-to-height ratio (r = 0.467). In contrast, BMI showed only a weak-to-moderate correlation with percent fat mass (r = 0.250), supporting the value of direct assessment of body composition beyond BMI alone.

Handgrip strength was weakly correlated with BMI (Spearman r = 0.069) and inversely correlated with fat mass percentage (r = -0.317), suggesting that muscle function captured information that cannot be reduced to adiposity alone. Changes in body weight were strongly correlated with changes in fat mass percentage (Spearman r = 0.865 in the analysis dataset) and only weakly correlated with changes in HbA1c (r = 0.042), consistent with the observation that glycemic and adiposity-related responses, although clinically related, do not necessarily evolve in parallel. Changes in weight and fat mass percentage were moderately correlated with changes in log-transformed CRP (r = 0.476 and r = 0.461, respectively), supporting a biologically plausible link between adiposity reduction and improvement in low-grade systemic inflammation.

Clinical studies increasingly emphasize that mean HbA1c reductions alone can mask substantial interpatient variability in response. The GRADE randomized trial (n = 5,047; mean follow-up 5 years; comparing add-on glargine, glimepiride, liraglutide, or sitagliptin to metformin in patients with diabetes duration< 10 years and baseline HbA1c 6.8–8.5%) showed all four drugs lowered HbA1c on average. Yet, a substantial proportion of participants across all arms failed to sustain target glycemic control (<7%) over time. Notably, even among those with the lowest baseline HbA1c stratum (6.8–7.2%), approximately 60% eventually experienced metabolic failure; this proportion increased progressively in higher baseline HbA1c strata (18, 19). Glargine and liraglutide were modestly but significantly more effective than glimepiride or sitagliptin in prolonging time below the glycemic threshold. However, all groups showed a gradual upward drift in HbA1c over the follow-up period. This underscores that many patients experience "metabolic failure" despite acceptable average drops, highlighting the need to evaluate responder rates and durability rather than just mean changes (20).

Recent real-world data reinforce this point. In a German/Austrian registry study of GLP-1 RAs (DPV register, n = 4,467), only 14% of patients achieved both a clinically meaningful HbA1c reduction (≥0.5%) and weight loss (≥5%) at 6 months. Notably, over one-third saw an HbA1c drop without weight loss, and another subset lost weight without an improvement in HbA1c (21). Such heterogeneity of treatment response means that a therapy's true benefit can be underappreciated if we look only at population averages (22).

Real-world comparative effectiveness data further contextualize these findings. A 2023 target-trial emulation using US Veterans Affairs electronic health records (n = 283,998) showed that, compared to SU, SGLT2i, GLP-1 RAs, and DPP-4i each significantly reduced the risk of major adverse cardiovascular events, with GLP-1 RAs and SGLT2i showing similar cardiovascular effectiveness (HR ~0.77–0.78 vs. sulfonylurea; no significant difference between these two classes), confirming both as robust second-line options with cardiometabolic advantages beyond glycemia alone (23). These findings complement the ADA 2026 consensus framework, which recommends individualized, cardiometabolic-risk-guided agent selection beyond a purely glucocentric approach, particularly for patients with obesity, established cardiovascular disease, or chronic kidney disease (24).

Alongside glycemic and anthropometric endpoints, systemic low-grade inflammation has emerged as a clinically relevant dimension in the evaluation of antidiabetic therapy. High-sensitivity C-reactive protein (hs-CRP) is now recognized as an independent predictor of cardiovascular mortality in T2DM, with each unit increase in log-transformed hs-CRP associated with significantly increased vascular and all-cause mortality risk, independent of established cardiometabolic risk factors (25). The inflammatory burden in T2DM is not homogeneous across treatment regimens: a 2025 systematic review and meta-analysis of 52 randomized controlled trials (n = 4,734) confirmed that GLP-1 RA therapy produces significantly greater reductions in circulating CRP compared with metformin (SMD −0.95; 95% CI −1.78 to −0.13) and other oral antidiabetic drugs (SMD −1.06; 95% CI −1.64 to −0.47), with effect magnitude increasing with treatment duration (26). By contrast, insulin-based regimens have not demonstrated consistent CRP-lowering effects, and sulfonylureas lack any documented direct anti-inflammatory mechanism (27). These differential inflammatory effects parallel and partly explain the divergent cardiometabolic outcomes observed across

drug classes and support the inclusion of inflammatory biomarkers alongside glycemic and body composition endpoints in comparative effectiveness studies.

This prospective cohort study was designed to evaluate antidiabetic treatment classes using a multidimensional outcome framework. Rather than focusing exclusively on mean change in glycemic control, the analysis integrated glycemic control, anthropometric and body composition parameters, handgrip strength, renal function, hs-CRP, response criteria, and sex-specific exploratory analyses. Accordingly, discussion of these findings should focus on the data showing that different metformin treatment regimens were associated with distinct cardiometabolic profiles over 12 months. The results obtained are observational in nature, and therefore, treatment contrasts should be interpreted as adjusted associations rather than causal effects.

In this study, antidiabetic therapies were associated with distinct glycemic, adipose, functional, and inflammatory profiles after adjustment for baseline outcomes and prespecified clinical covariates. The main finding was a consistent multivariate association for GLP-1 RA therapy: compared with metformin monotherapy, GLP-1 RA therapy was associated with lower HbA1c at 12 months, lower body weight, BMI, and waist circumference, lower fat mass percentage, and lower log-transformed hs-CRP, with no significant adverse differences in handgrip strength or eGFR. These results support the concept that, in routine endocrine care, treatment assessment in T2DM should extend beyond HbA1c and incorporate adiposity, muscle function, and low-grade inflammation as clinically relevant outcome dimensions.

The glycemic findings are consistent with the established efficacy of incretin-based therapy, but the present analysis adds two important real-world qualifications. First, the adjusted treatment models showed that GLP-1 RA therapy had the largest favorable HbA1c effect compared with metformin (adjusted β = -0.745 percentage points; 95% CI, -0.856 to -0.634; FDR $q < 0.001$), while SGLT2i and insulin were also associated with lower adjusted HbA1c at 12 months. Second, responder analyses showed that target attainment and combined metabolic response were not fully captured by mean HbA1c change alone. Although sparse events produced very wide confidence intervals in logistic models, the descriptive pattern was clinically informative: the combined endpoint of HbA1c reduction $\geq$ 0.5 percentage points together with weight loss $\geq$ 5% was observed in 87.0% of GLP-1 RA-treated patients and was almost absent in the other groups. This reinforces the idea that the response to antidiabetic therapy is multidimensional and that glycemic and weight responses should be interpreted together rather than as isolated outcomes (28, 29).

Body composition outcomes provided the strongest extra-glycemic signal in the study. GLP-1 RA therapy was associated with the greatest adjusted reduction in body weight (β = -5.246 kg vs. metformin; 95% CI -5.921 to -4.572; FDR $q < 0.001$) and percent fat mass (β = -2.731 percentage points; 95% CI -3.266 to -2.195; FDR $q < 0.001$). SGLT2i showed an intermediate favorable profile for weight, BMI, waist circumference, and fat mass, whereas insulin and SU were associated with less favorable adiposity trajectories. This hierarchy is biologically plausible: GLP-1 RAs reduce appetite, energy intake, and fat mass; SGLT2i induce modest caloric loss through glucosuria; and insulin and sulfonylureas may promote or facilitate weight gain in susceptible patients (30, 31). It is important to note that separating SU and DPP-4i in the statistical analysis avoids the pharmacological ambiguity of the previous SU/DPP-4i combination treatment arm and allows for a more cautious interpretation of these smaller subgroups.

A major clinical concern with weight-loss therapies is whether body weight reduction is accompanied by impairment of muscle function (32, 33). In this cohort, handgrip strength remained stable across treatment groups, and the adjusted contrast of GLP-1 RA versus metformin was nearly null (β = +0.273 kg; 95% CI -0.579 to +1.124; FDR $q = 0.731$). Analyses of lean mass and skeletal muscle mass also provided no evidence of a clinically meaningful adverse functional effect after correction for multiplicity. These findings do not directly prove muscle preservation, as grip strength is only one functional assessment criterion, and bioimpedance is less accurate than DEXA for compartmental analysis. However, the combination of reduced fat mass and stable handgrip strength suggests that the observed weight loss was not accompanied by measurable deterioration in upper limb muscle function over the 12-month follow-up period. This observation is consistent with the literature showing that weight loss associated with GLP-1 RA is often predominantly adipose. At the same time, functional consequences depend on age, baseline frailty, protein intake, and resistance exercise (34, 35).

The inflammatory findings extend the metabolic interpretation. Because hs-CRP was measured using a highly sensitive method and analyzed after logarithmic transformation, it provides a valid marker of low-grade systemic inflammation in this cohort. GLP-1 RA therapy was associated with a lower adjusted ln(hs-CRP) at 12 months compared with metformin (β = -0.459; 95% CI -0.828 to -0.090; FDR $q = 0.038$), corresponding to an adjusted hs-CRP level that was approximately 36.8% lower. SGLT2i showed a nominally favorable hs-CRP contrast, but this did not remain significant after FDR adjustment.

These results are consistent with the known association between adipose tissue reduction and improvement in inflammatory burden (36). In addition, mechanistic data suggest that GLP-1 RA therapy may attenuate inflammatory signaling by modulating adipose tissue macrophage activity, NF-kappaB-related pathways, and cytokine production (37-39). However, the observational design precludes attribution of a direct effect of the anti-inflammatory drug. Therefore, the improvement in inflammation should be interpreted as an adjusted association that may reflect both adiposity reduction and class-specific pleiotropic mechanisms.

The insulin group illustrates the importance of interpreting treatment profiles in a clinical context. Insulin was associated with a lower adjusted HbA1c at 12 months compared with metformin, but was also associated with an unfavorable profile of weight, BMI, waist circumference, and fat mass. This should not be interpreted as evidence of the intrinsic inferiority of insulin, as insulin was prescribed in a real-world setting to patients who may have had more advanced beta-cell failure, a higher glycemic burden, a longer disease course, or greater clinical complexity (40, 41). Rather, the finding highlights confounding factors by indication and the distinct clinical role of insulin compared with weight-loss therapies. Similarly, the SU and DPP-4i groups were small and should be interpreted with caution; SU was associated with weight and fat mass patterns consistent with its known clinical profile, whereas DPP-4i appeared weight-neutral but was below statistical power to draw firm conclusions (42).

Although a greater response to GLP-1 RA was hypothesized in men, sex-specific analyses showed generally similar reductions in HbA1c, weight loss, and fat mass reduction in women and men treated with GLP-1 RA (43). Formal testing of treatment-sex interaction was not significant for HbA1c, weight, fat mass, handgrip strength, or ln(hs-CRP). Therefore, results stratified by sex should be considered descriptive and hypothesis-generating rather than evidence of treatment efficacy that differs by sex.

Correlation analyses also support the multidimensional structure of the study. The expected internal correlations between triglycerides and VLDL cholesterol, total cholesterol and LDL-C, and urinary albumin and the albumin-to-creatinine ratio support the consistency of the data. More importantly, BMI was only weakly to moderately correlated with percent fat mass, and handgrip strength was not reducible to BMI or adiposity alone. Changes in weight and fat mass were correlated with changes in log-transformed CRP, whereas weight changes were only weakly correlated with changes in HbA1c. These patterns reinforce the central methodological premise of the study: HbA1c, weight, fat mass, muscle function, and inflammatory burden capture overlapping but nonidentical dimensions of the endocrine-metabolic phenotype (44).

Strengths and limitations

The main strengths of this study are the prospective follow-up design, the use of individual patient data, standardized clinical and laboratory assessments, direct measurement of body composition, handgrip dynamometry, and measured hs-CRP. The statistical analysis also strengthens the manuscript by separating SU and DPP-4i, adjusting each continuous endpoint for its baseline value, using robust standard errors, and applying FDR correction to secondary comparisons.

Several substantial limitations remain. Treatment allocation was not randomized and reflected routine clinical decisions, making confounding by indication inevitable. Although the models were adjusted for baseline outcomes and relevant clinical covariates, residual confounding may persist depending on disease severity, cardiovascular risk, renal status, treatment dose, treatment adherence, diet, physical activity, socioeconomic status, and clinician prescribing preferences. No propensity score matching, inverse probability weighting, or emulation of target trials was performed. Therefore, all treatment contrasts should be interpreted as adjusted associations, not as comparative causal estimates of efficacy.

The per-protocol nature of the analysis is another limitation. Only patients who completed the 12-month follow-up period and remained on the same treatment regimen were included in the primary analysis. This improves the consistency of exposure but may overestimate efficacy, as patients who discontinued, switched therapy, or were lost to follow-up may have had poorer tolerability, adherence, or response. The comparison between included and eligible but excluded patients suggested generally similar baseline values for HbA1c, weight, BMI, fat mass, and hs-CRP, but differences in age and eGFR indicate that selection effects cannot be ruled out.

The size of the subgroups is also important. The SU and DPP-4i groups were small, and the response patterns for rare endpoints generated very wide confidence intervals. Therefore, the responder analyses should be considered clinically descriptive and hypothesis-generating. The study was not powered *a priori* for sex-treatment interactions, renal endpoints, handgrip scores, or inflammatory outcomes. Bioimpedance provides practical estimates of body composition in routine care but does not replace DEXA or imaging-based assessment of visceral adiposity and lean tissue. Handgrip strength is clinically useful but cannot fully characterize sarcopenia, lower limb function, or muscle quality. Finally, the single-center tertiary care setting may limit generalizability to primary care, rural, or less intensively managed populations. In addition, the cohort had a

relatively high mean baseline hs-CRP, and because a conventional exclusion threshold of > 10 mg/L was not separately applied, occult infection or comorbidity cannot be fully excluded as contributors to the inflammatory findings despite adjustment for recent infection.

Clinical implications and future directions

Despite these limitations, the findings have practical implications for endocrine care. They suggest that in patients with obesity-related type 2 diabetes (T2DM), treatment evaluation should not be limited to HbA1c alone (45). A therapy may improve glycemia while worsening or failing to improve adiposity. In contrast, a weight-loss therapy may yield benefits better captured by combined metabolic endpoints that integrate glycemic control, adiposity, and functional outcomes (45, 46). In this cohort, GLP-1 RA therapy had the most favorable combined profile across glycemic, adiposity, and inflammatory outcomes, while preserving measured muscle strength and renal stability over a 12-month period. SGLT2i had an intermediate favorable cardiometabolic profile, particularly for weight and adiposity, whereas insulin and SU patterns require interpretation in light of disease severity and treatment indication.

Future studies should validate these findings in larger multicenter cohorts with predefined sample size calculations, longer follow-up, systematic data on dose and adherence, structured assessment of diet and physical activity, and more granular characterization of cardiovascular and renal disease. Randomized designs, propensity-based observational designs, or target trial emulations would help to separate pharmacological effects from effects of treatment selection. Future work should also include DEXA- or imaging-based body composition assessment, repeated measurements of hs-CRP and additional inflammatory cytokines, and functional outcomes beyond handgrip strength (47, 48). Such studies would clarify whether the multidimensional profile observed here translates into durable reductions in cardiometabolic risk and functional decline.

Conclusions

Taken together, these findings support a multidimensional approach to assessing outcomes in obesity-associated T2DM, integrating HbA1c with body composition, muscle function, renal stability, and high-sensitivity inflammatory markers. After adjusting for baseline outcomes and relevant clinical covariates, GLP-1 RA therapy had the most favorable multidimensional profile, with lower values for HbA1c, body weight, BMI, waist circumference, percent fat mass, and log-transformed hs-CRP compared with metformin monotherapy. These associations occurred without measurable deterioration in handgrip strength or eGFR. SGLT2 inhibitors showed an intermediate favorable cardiometabolic profile, particularly with respect to weight and adiposity. In contrast, the insulin and sulfonylurea models require interpretation in light of disease severity, treatment indication, and residual confounders. The DPP-4 inhibitor subgroup was small and should be considered descriptive rather than inferential. Analyses stratified by sex did not demonstrate significant interactions between treatment and sex, and analyses of responders should be interpreted primarily descriptively, as rare events produced unstable logistic estimates. The results require confirmation in larger multicenter cohorts or pragmatic randomized clinical trials before they can be used to support therapeutic prioritization.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Carol Davila University of Medicine and Pharmacy, Bucharest (approval no. 1514, dated 03.06.2022) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

AI use disclosure

During the preparation of this manuscript, the authors used an AI-based language tool for grammar verification, translation assistance, and finding appropriate references. The authors reviewed and edited all output and take full responsibility for the content.

Conflict of interest

The authors declare no conflict of interest.

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