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# Short-term effects of low-dose tirzepatide on lipid profile, glucose homeostasis and hepatic steatosis index in adults with obesity, but without diabetes mellitus: a prospective observational study

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ABSTRACT

*Background/aims:* Tirzepatide has been approved for weight loss in adults with obesity. However, real-world data are still needed. This real-world prospective study is among the first to evaluate the short-term metabolic effects of low-dose tirzepatide in adults with obesity but without diabetes mellitus (DM). Secondary endpoints included associations between these changes and anthropometric or baseline metabolic parameters.

*Methods:* In this prospective observational study, adults with obesity but without diabetes mellitus received tirzepatide (2.5 mg/week, escalating to 5 mg/week, subcutaneously) for 12 weeks. Body weight, body mass index (BMI), total (TC), low-density (LDL-C) and high-density lipoprotein cholesterol (HDL-C), triglycerides, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and hepatic steatosis index (HSI) were measured at baseline and week 12.

*Results:* Seventy-five participants (mean age 46.9 ± 9.9 years) were included. After 12 weeks, body weight (−8.1 ± 4.3 %) and BMI significantly decreased. TC, LDL-C, triglycerides, FPG, HbA1c, and HSI were significantly reduced and inversely associated with their baseline levels. HbA1c and HSI changes correlated with weight loss. No effect was observed on HDL-C. Statin use had no impact on outcomes.

*Conclusion:* Short-term low-dose tirzepatide improves the lipid profile, HbA1c, and HSI in obese adults without DM, especially in those with abnormal baseline values. Lipid changes occurred independently of weight loss.

## 1. Introduction

Tirzepatide is a novel dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, developed for the treatment of type 2 diabetes mellitus (T2DM). In large-scale clinical trials, tirzepatide has demonstrated significant efficacy in improving glycemic control and inducing substantial weight loss.[1,2] These effects have led to its approval not only for glycemic management in T2DM, but also for the treatment of obesity, irrespective of glycemic status.[4] Tirzepatide has been included among next-

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generation pharmacotherapies for obesity, alongside GLP-1 receptor agonists and combination therapies, due to its promising efficacy and tolerability.[5]

While the glycemic effects of tirzepatide have been well-documented, growing attention has been paid to its broader cardiometabolic benefits, particularly regarding lipid metabolism. Dyslipidemia is a common feature of both T2DM and obesity and represents a major modifiable risk factor for cardiovascular disease.[6] Therefore, agents capable of targeting multiple components of the cardiometabolic spectrum are of considerable clinical interest.[7–9]

Data from the SURPASS (A Study of Tirzepatide [LY3298176] versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants with Type 2 Diabetes) clinical program (a series of phase 3 clinical studies evaluating tirzepatide in people with T2DM and related metabolic conditions) have shown that tirzepatide can significantly decrease total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, while leading to an increase in high-density lipoprotein cholesterol (HDL-C) when treatment duration is extended.[10–12] These effects appear to be dose-dependent and partly mediated through weight reduction and improved insulin sensitivity. Notably, favorable lipid changes have also been observed in individuals without DM. For example, the SURMOUNT-1 (clinical trials evaluating once-weekly tirzepatide for chronic weight management) trial demonstrated significant reductions in visceral adiposity and improvements in lipid profiles in participants with obesity, but without DM, receiving tirzepatide.[2] Moreover, in SURMOUNT-1, the weight reduction also led to improvements in fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), even in those with normal baseline glycemic levels.[2]

These landmark trials confirm the broad metabolic efficacy of tirzepatide across different populations. The SURPASS program demonstrated consistent, dose-dependent improvements in glycemic control and lipid parameters in patients with T2DM, while the SURMOUNT-1 trial showed similar metabolic benefits, including lipid and glycemic improvements, in non-diabetic individuals with obesity.[2]

However, despite these promising results, real-world data remain limited—especially in non-diabetic populations. So far, no such study has been conducted in Greece. The primary aim of our study was to address this gap by providing short-term, real-world evidence of tirzepatide's metabolic effects in obese adults without diabetes. We further investigated the short-term effects of low-dose tirzepatide on lipid and glucose metabolism, as well as on liver disease and kidney function. Although all participants were normoglycemic, HbA1c was assessed to explore potential glycemic effects of tirzepatide even within the non-diabetic range, as previously suggested in randomized clinical trials.[2] Secondary aims were to explore potential associations of these changes with anthropometric parameters and baseline lipid levels.

## 2. Materials and methods

### 2.1. Patients and study protocol

This was a prospective, multicenter cohort study conducted across ten metabolic outpatient clinics in Greece, including four centers in the capital city (Athens), one in Central Greece (Larissa), two in Northern Greece (Thessaloniki and Kavala), one in Southern Greece (Patras), and two on the island of Crete (Chania and Rethymno).Participants were consecutively recruited during routine outpatient visits at each center between January and April 2025. Eligible individuals were informed about the study and provided written informed consent. Inclusion criteria were: age $\geq$ 18 years, body mass index (BMI) $\geq$30 kg/m$^2$, absence of DM (HbA1c <6.5 %, FPG <126 mg/dL), and no use of glucose-lowering medications. Exclusion criteria were: familial hypercholesterolemia or hypertriglyceridemia, chronic kidney disease stage $\geq$3, active liver disease and personal or family history of medullary thyroid carcinoma. Tirzepatide was administered subcutaneously once weekly, starting at 2.5 mg for the first four weeks and followed by a dose of 5 mg/week for the remaining eight weeks. Participants were instructed to maintain their usual dietary and physical activity habits.

### 2.2. Measurements

Anthropometric measurements (weight and height) were obtained at baseline and at week 12 using standardized procedures. BMI was calculated accordingly. Fasting blood samples were collected at both time points to assess FPG, HbA1c, lipid profile (TC, LDL-C, HDL-C, triglycerides), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), hepatic steatosis index (HSI) and estimated glomerular filtration rate (eGFR). HSI was calculated using the formula HSI = 8 * (ALT/AST ratio) + BMI + 2 (if female) + 2 (if diabetes mellitus),[13] whereas eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14]

All laboratory determinations were carried out after an overnight fast in local laboratories using standard methods. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the Hellenic Endocrine Network (Approval No.: N2024/0121316). Additionally, the study was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) under the identifier ACTRN12625000071426. Written informed consent was obtained from all participants prior to their enrollment. The Hellenic Endocrine Network is a clinician-led society, and the authors attached to it are practicing endocrinologists whose main activities combine patient care with clinical research and professional education.

### 2.3. Statistical analysis

Data were tested for normality using the D'Agostino-Pearson test. Values were expressed as mean ± standard deviation (SD) or median (interquartile range - IQR) for variables. Paired *t*-tests or Wilcoxon signed-rank tests were applied as appropriate. Associations between percentage weight reduction and changes in lipid profile, HbA1c and eGFR were evaluated using Pearson or Spearman correlation analyses. Subgroup analyses were performed based on sex and baseline values. Statistical significance was defined as a two-sided *P*-value <0.05. All analyses were performed using the Statistical Package for Social Sciences (SPSS) software (version 28.0; SPSS Inc., Chicago, IL, USA).

## 3. Results

Seventy-five patients were included (mean age 46.9 ± 9.9 years; mean baseline body weight and BMI 114.1 ± 25.4 kg and 38.9 ± 7.7 kg/m$^2$, respectively). The demographic and laboratory parameters at baseline and at 12 weeks of treatment are presented in Table 1. Adverse events were mild and infrequent.

Among the 75 participants, 10 individuals (13.3 %) reported transient gastrointestinal symptoms during the initial treatment phase. Specifically, nausea was reported by 7 participants (9.3 %), abdominal discomfort by 2 participants (2.7 %), and diarrhea by 1 participant (1.3 %). Notably, no participant discontinued tirzepatide due to adverse effects, likely reflecting the favorable tolerability of the low-dose regimen (up to 5 mg/week) during the 12-week period.

Tirzepatide treatment led to a significant decrease in body weight (8.1 ± 4.3 %; $P < 0.001$), BMI (−3.1 ± 1.7, $P < 0.001$), TC (mean change: −15.3 ± 35.7 mg/dL; $P < 0.001$), LDL-C (mean change: −9.8 ± 20.0 mg/dL; $P < 0.001$), triglycerides (mean change: −10.9 ± 37.5 mg/dL; $P = 0.011$), FPG (median change:–3.9, IQR: 8 mg/dL; $P < 0.001$), HbA1c (mean change: −0.12 ± 0.61 %; $P < 0.001$) and eGFR (mean change: −4.3 ± 11.8 mL/min/1.73m$^2$; $P = 0.02$). There was no significant effect on HDL-C levels. Changes in lipid profile and HbA1c are illustrated in Figs. 1 and 2, respectively.

Baseline LDL-C levels were inversely associated with LDL-C change ($r = -0.475$, $P < 0.001$), indicating that higher initial LDL-C

**Table 1**
Demographic and laboratory parameters at baseline and at 12 weeks of treatment with tirzepatide.

| Parameter | Age (years) | Body weight (kg) | | BMI (kg/m$^2$) | | TC (mg/dL) | | LDL-C (mg/dL) | | Triglycerides (mg/dL) | | HDL-C (mg/dL) | | FPG (mg/dL) | | HbA1c (%) | | AST | | ALT | | HSI | | eGFR (mL/min/1.73 m$^2$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | B | T | B | T | B | T | B | T | B | T | B | T | B | T | B | T | B | T | B | T | B | T | B | T |
| Mean | 46.85 | 114.1 | 105.1 | 39.9 | 36.8 | 190.1 | 177 | 115.8 | 106 | 130.2 | 119.2 | 48.3 | 47.8 | 112 | 107 | 5.6 | 5.4 | 24 | 22.1 | 30.2 | 29.4 | 51.4 | 48.1 | 107.1 | 103.6 |
| Median | 49 | 111 | 103 | 39.0 | 35.7 | 187.8 | 177.6 | 31.2 | 29 | 58 | 44.5 | 10.4 | 9.3 | 112 | 106 | 5.6 | 5.4 | 22 | 21 | 27 | 25 | 51 | 47.1 | 97.9 | 95.5 |
| SD | 9.89 | 25.4 | 25.6 | 7.8 | 7.9 | 36.9 | 32.7 | 112.0 | 105.5 | 116.5 | 113.0 | 47.0 | 48.0 | 8.2 | 8.5 | 0.31 | 0.3 | 10.5 | 8.6 | 14 | 14.4 | 8.2 | 8.9 | 34.37 | 28.25 |
| Minimum | 25 | 71 | 58 | 26.7 | 21.8 | 78 | 66.6 | 25 | 25 | 41 | 28 | 29 | 32 | 82 | 86 | 4.5 | 4.6 | 9 | 9 | 6 | 7 | 37.4 | 15.3 | 60 | 66.8 |
| Maximum | 73 | 206.4 | 206.4 | 74.9 | 74.9 | 296.2 | 269.8 | 190 | 181 | 374 | 253 | 79 | 67 | 125 | 122 | 6.3 | 6 | 65 | 57 | 80 | 89 | 73.6 | 72.8 | 236 | 217 |
| IQR | 11.5 | 30.8 | 27.8 | 9.69 | 9.6 | 36.7 | 41.8 | 39.25 | 36.00 | 58.8 | 55.50 | 12.5 | 13.0 | 14.4 | 10.2 | 0.46 | 0.4 | 9.5 | 10 | 20 | 21.8 | 10.3 | 10.1 | 20.95 | 19 |
| *P* | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | 0.013 | | 0.697 | | <0.001 | | <0.001 | | 0.04 | | 0.351 | | <0.001 | | 0.002* | |

**Abbreviations:** ALT: alanine transaminase; AST: aspartate aminotransferase; B: baseline; BMI: body mass index; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; HSI: Hepatic Steatosis Index; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation; T: post-treatment; TC: total cholesterol; TG: triglycerides. *P*: t-test for paired samples; *P**: Wilcoxon non-parametric test.

concentrations were associated with a more pronounced reduction compared with lower levels. Similar inverse correlations were observed between baseline triglycerides and their change (r = −0.642, $P < 0.001$). No significant correlations were found between these changes and the percentage in weight reduction or baseline BMI.

There was a modest reduction (−2 ± 7.7 IU/L; $P = 0.038$) or no effect (−0.9 ± 8.1 IU/L; $P = 0.329$) of tirzepatide on AST and ALT activities, respectively. However, a significant decrease in HSI levels was observed (mean change: −3.3 ± 5.1; $P < 0.001$) levels.

Regarding HbA1c, higher baseline levels were strongly associated with greater reductions (r = −0.33, $P = 0.004$). Moreover, a significant correlation was observed between percentage weight decrease and HbA1c change (r = 0.31, $P = 0.006$), suggesting that the greater the weight loss, the greater the improvement in glycemia. These associations were particularly evident among female participants (n = 55, r = 0.33, $P = 0.019$), but not for males (n = 23, r = 0.30, $P = 0.172$) (Fig. 3). However, this gender effect may relate to statistical power (number of participants in each group: 55 vs 23). No associations were found between HbA1c reduction and age, eGFR, HDL-C, LDL-C, triglycerides, or baseline BMI.

There was also a significant negative correlation between the percentage of body weight change with the change in HSI (r = −0.4, $P = 0.001$). Notably, no association between weight reduction and eGFR change was observed.

The demographic and laboratory parameters according to statin use are presented in Table 2. No differences were observed in percentage weight reduction ($P = 0.326$), LDL-C ($P = 0.323$), triglycerides ($P = 0.143$), FPG ($P = 0.881$), HbA1c ($P = 0.908$) and HSI ($P = 0.301$) levels between the two groups. When analyzed with the Mann-Whitney *U* test, the difference in HDL-C change between groups was not statistically significant ($P = 0.175$). The within-group changes were also not significant [median change −0.5 mg/dL (IQR 6.8, $P = 0.128$) in patients receiving statins and − 1 mg/dL (IQR 4, $P = 0.365$) in those without treatment].

In a *post-hoc* analysis, participants were classified as prediabetic or normoglycemic using both FPG and HbA1c criteria. Based on baseline FPG, 70 participants (93.3 %) met criteria for prediabetes. These individuals showed greater mean reductions in FPG [−2.87 (5.74)] and HbA1c [−0.19 (0.2) %] than normoglycemics [n = 5; FPG: −0.9 (2.87) mg/dL; HbA1c: −0.1 (0.1) %], but differences were not statistically significant (FPG: $P = 0.07$, HbA1c: $P = 0.122$).

Using baseline HbA1c (5.7–6.4 %), 22 participants (29.3 %) were classified as prediabetic and 53 (70.7 %) as normoglycemic. In this categorization, prediabetic participants demonstrated a significantly greater reduction in HbA1c [−0.2 (0.2) %] compared with normoglycemics (−0.1 (0.3) %; $P = 0.023$), while FPG reduction remained statistically nonsignificant [−5.74 (5.74) vs −2.87 (7.75) mg/dL; $P = 0.144$].

## 4. Discussion

This is the first study in the Greek population demonstrating that short-term administration of low-dose tirzepatide in obese individuals without DM, leads to amelioration in lipid metabolism (TC, LDL-C, triglycerides, but not HDL-C), glucose homeostasis (FPG, HbA1c) and HSI. These reductions were inversely associated with their baseline levels and, except for HbA1c, they were independent of the degree of weight loss or the use of statins.

Long-term studies from the SURPASS program have consistently shown durable reductions in TC, LDL-C and triglycerides, with accompanying increases in HDL-C, sustained over periods of 40–72 weeks.[10–12] These changes appear to be dose-dependent and closely linked to the weight-reducing and insulin-sensitizing effects of tirzepatide.

The favorable effect of tirzepatide on lipid metabolism has also been demonstrated in a meta-analysis including 7151 patients participating in seven randomized controlled trials with a minimum duration of 12

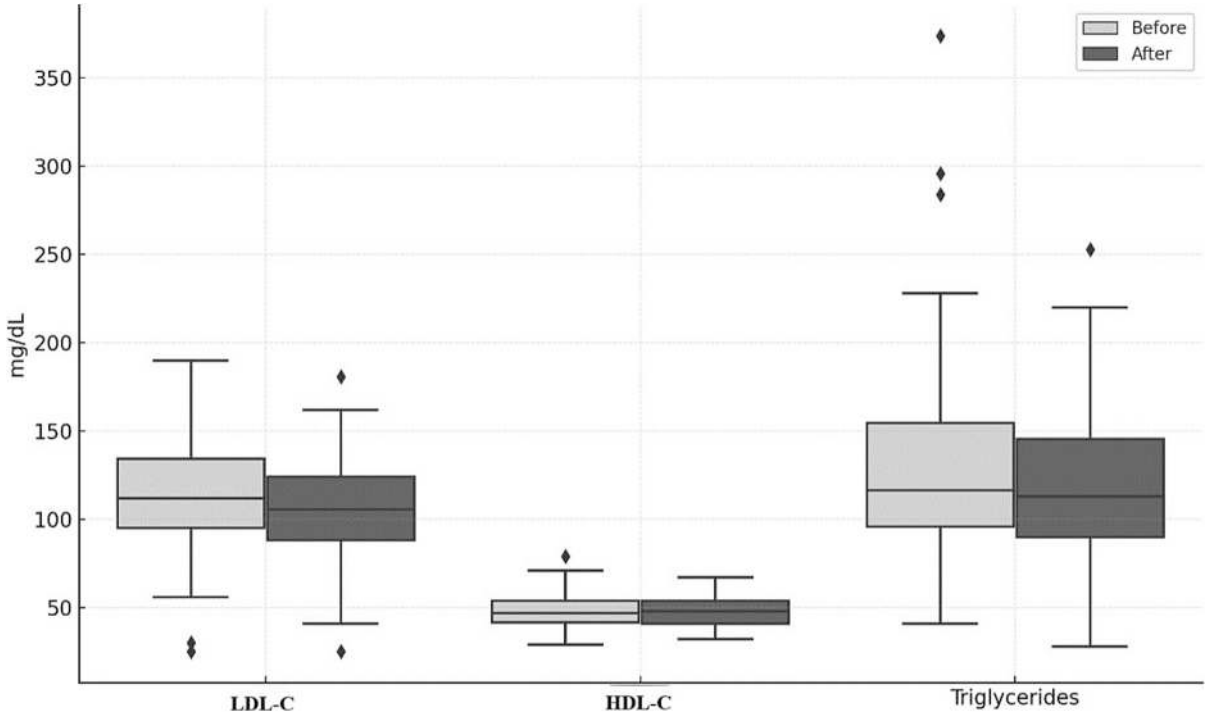


**Fig. 1.** Changes in lipid levels at baseline and after 12 weeks of treatment with tirzepatide.
Boxplots showing lipid levels before and after 12 weeks of tirzepatide treatment in adults with obesity, but without diabetes (n = 75). Paired data are displayed for low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Boxes represent the interquartile range (IQR), horizontal lines indicate medians, and whiskers denote 1.5 × IQR. Paired comparisons were analyzed using the Wilcoxon signed-rank test due to non-normal distribution of differences. LDL-C and TG levels decreased significantly ($P < 0.05$), while HDL-C remained unchanged ($P > 0.05$).

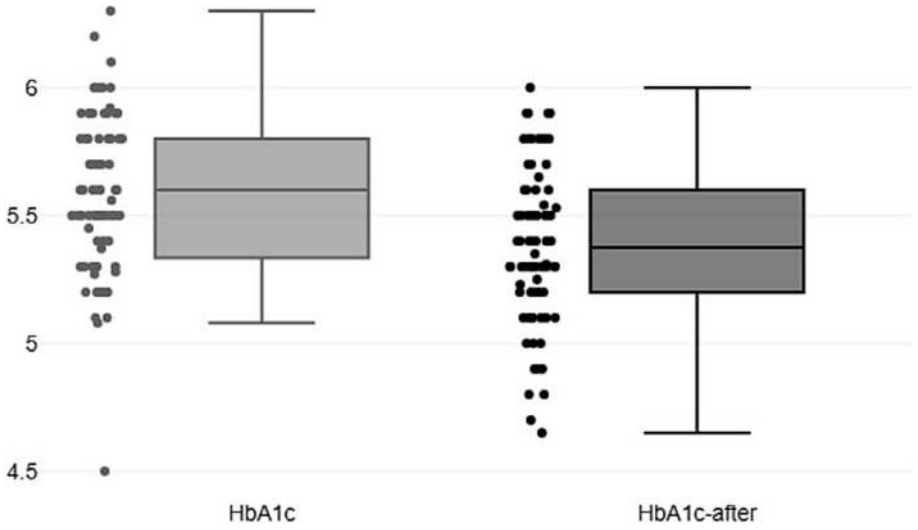


**Fig. 2.** Change in glycated hemoglobin (HbA1c) before and after 12 weeks of treatment with tirzepatide.
Boxplot illustrating the distribution of glycated hemoglobin (HbA1c) values in adults with obesity but without diabetes (n = 75) before (HbA1c) and after (HbA1c-after) 12 weeks of tirzepatide therapy. Boxes represent the interquartile range (IQR), horizontal lines indicate medians, and whiskers correspond to 1.5 × IQR. Individual data points are overlaid.

weeks.[3] Tirzepatide (in maintenance doses of 5, 10 and 15 mg per week) was associated with significant reductions in TC, LDL-C, very-low-density lipoprotein cholesterol (VLDL-C), and triglyceride concentrations, and with an increase in HDL-C levels after 12 weeks of therapy ($P < 0.005$). These results further affirm the potential of tirzepatide to modulate lipid metabolism within a short timeframe. Furthermore, Schiavo et al. (2025) demonstrated that combining tirzepatide with a ketogenic low-energy diet produced substantial lipid benefits, by increasing HDL-C and reducing triglyceride and TC levels, reinforcing its efficacy in targeting dyslipidemia.[15] To date, there are no published studies investigating the combined effect of tirzepatide and the Mediterranean diet in patients with obesity or metabolic disorders; the only ongoing trial is a recently initiated phase IV study (ClinicalTrials.gov NCT06774079) in Crohn's disease patients that incorporates tirzepatide alongside a Mediterranean dietary intervention. Although no structured dietary data were collected, it is plausible that elements of the

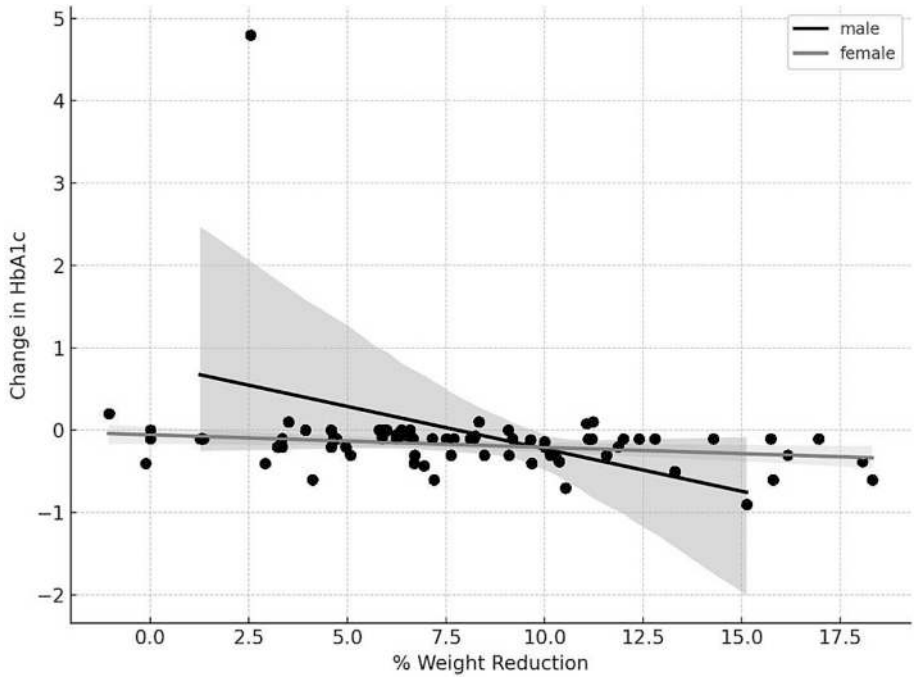


**Fig. 3.** Association between weight reduction and change in HbA1c, stratified by sex.
Scatter plot illustrating the relationship between percentage weight reduction and change in glycated hemoglobin (HbA1c) following 12 weeks of tirzepatide therapy. Each dot represents an individual participant (n = 75), with linear regression lines shown separately for males (black line) and females (gray line). Shaded areas represent 95 % confidence intervals. HbA1c change is expressed as the absolute difference (after – before), where negative values reflect improvement. Greater weight loss correlated with greater HbA1c reductions (r = 0.31, $P = 0.006$), achieving significance in women (r = 0.33) but not in men (r = 0.30).

Mediterranean diet—typical of the Greek population—may have contributed to the observed metabolic outcomes in our population.

Furthermore, the SURMOUNT-1 trial in individuals with obesity, but not DM, demonstrated improvements in lipid profile, as well as reductions in visceral adiposity and waist circumference.[2] These findings, along with additional analyses showing favorable changes in apolipoprotein profiles and atherogenic lipoprotein particles,[7,16] suggest that tirzepatide may exert cardiometabolic benefits via several pathways.

Mechanistically, tirzepatide is believed to influence lipid metabolism both through direct and indirect mechanisms involving multiple metabolic pathways. In particular, by activating both the GIP and GLP-1 receptors, tirzepatide enhances β-cell function and improves insulin sensitivity,[17] thereby reducing hepatic de novo lipogenesis and promoting peripheral lipid clearance.[18] Improved insulin sensitivity attenuates adipose tissue lipolysis, leading to decreased circulating free fatty acid flux to the liver, which, in turn, reduces hepatic triglyceride synthesis and VLDL secretion.[19] Concurrently, tirzepatide has been shown to reduce hepatic steatosis, by reducing fatty acid uptake, promoting cholesterol excretion, and enhancing mitochondrial-lysosomal function.[20] The substantial weight loss induced by tirzepatide further contributes to improvements in lipid profile by decreasing visceral adiposity, increasing HDL-C concentrations and lowering triglycerides and small dense LDL particle levels, which are highly atherogenic.[21] Collectively, these mechanisms not only account for the observed lipid improvements but also highlight the integrated cardiometabolic benefits associated with tirzepatide therapy.[11,12,15,22]

The effect of tirzepatide on glucose metabolism suggests potential therapeutic implications in early metabolic modulation and DM prevention. Recent clinical evidence suggests that tirzepatide may even facilitate the achievement of normoglycemia in patients with T2DM, raising the possibility of pharmacologically induced diabetes remission.[23] The underlying mechanisms include dual receptor agonism, which promotes insulin secretion, suppresses glucagon secretion, delays gastric emptying, and enhances satiety.[24] Collectively, these actions contribute to improved glucose homeostasis, positioning tirzepatide as a promising candidate for early intervention in individuals at risk for metabolic disorders before the onset of overt hyperglycemia. In our *post-hoc* subgroup analysis, individuals with baseline prediabetes—particularly when defined by HbA1c 5.7–6.4 %—exhibited significantly greater reductions in HbA1c compared with normoglycemics. This finding suggests that tirzepatide may exert enhanced glycemic effects even in the absence of overt diabetes, especially in individuals with subclinical dysglycemia. Although differences in FPG reduction were not statistically significant, the trends were consistent across both classification criteria (FPG and HbA1c), supporting a potential role for tirzepatide in early metabolic intervention. However, it should be noted that the mean reduction in HbA1c in the overall cohort was modest (−0.1 %), and thus of limited clinical significance in normoglycemic individuals. It should also be noted that the prediabetes analysis is based on relatively small numbers in the subgroups.

Our study demonstrated a statistically significant reduction in HSI after 12 weeks of treatment with tirzepatide, suggesting a favorable effect on hepatic steatosis in individuals with metabolic dysfunction. Although our study did not include histological assessment and the intervention period was notably shorter than that of the Study of Tirzepatide in Participants With Non-alcoholic Steatohepatitis (SYNERGY-NASH) trial (12 vs 52 weeks), the observed improvement in HSI aligns with the histologically confirmed resolution of metabolic dysfunction-associated steatohepatitis (MASH) without worsening of fibrosis in 44–52 % of patients treated with tirzepatide 5 mg in the SYNERGY-NASH trial, compared with 10–13 % in the placebo group ($P < 0.001$).[25] In the aforementioned study, an improvement in liver fibrosis by at least one stage without worsening of MASH was observed in approximately 51 % of patients receiving tirzepatide 5 mg/week.

Beyond hepatic fat reduction, emerging evidence suggests that tirzepatide may exert beneficial effects on ectopic fat depots in other organs. In the SUMMIT Cardiac Magnetic Resonance sub study (SUMMIT CMR), tirzepatide significantly reduced left ventricular (LV) mass and paracardiac adipose tissue in patients with obesity-related heart failure, highlighting its potential to reverse cardiac structural and adipose

**Table 2**
Demographic and lipid profile parameters by statin use.

| Parameter | Statin therapy (n = 18) | No statin therapy (n = 57) | *P* value |
|---|---|---|---|
| Age (years) | 52.5 (9) | 45.5 (12.5) | 0.001 |
| Pre-treatment weight (kg) | 102.4 (30) | 112 (28) | ns |
| Post-treatment weight (kg) | 95 (30) | 104 (25) | ns |
| % Weight reduction | −6.9 (5.3) | −7.6 (5.4) | ns |
| Pre-treatment BMI (kg/m$^2$) | 36.2 (8.3) | 39.8 (9.5) | ns |
| Post-treatment BMI (kg/m$^2$) | 34.8 (6.4) | 36.4 (9.5) | ns |
| Pre-treatment LDL-C (mg/dL) | 94 (25.8) | 119.5 (29) | 0.003 |
| Post-treatment LDL-C (mg/dL) | 81 (26) | 115 (27) | 0.001 |
| LDL-C change (mg/dL) | −16 (23.3) | −5 (10) | ns |
| Pre-treatment HDL-C (mg/dL) | 47 (13) | 46 (9.8) | ns |
| Post-treatment HDL-C (mg/dL) | 48 (10.3) | 48 (14) | ns |
| HDL-C change (mg/dL) | −0.5 (6.8) | −1 (4) | ns |
| Pre-treatment TG (mg/dL) | 126.5 (35) | 113 (62) | ns |
| Post-treatment TG (mg/dL) | 107.5 (34) | 115 (62) | ns |
| TG change (mg/dL) | −9 (41.8) | −6 (21) | ns |
| Pre-treatment FPG (mg/dL) | 109 (17.2) | 109 (11.5) | ns |
| Post-treatment FPG (mg/dL) | 99.4 (4.6) | 99.7 (14.4) | ns |
| FPG change (mg/dL) | −3.9 (12.5) | −3.9 (5.7) | ns |
| Pre-treatment HbA1c (%) | 5.6 (0.5) | 5.6 (0.4) | ns |
| Post-treatment HbA1c (%) | 5.3 (0.2) | 5.4 (0.4) | ns |
| HbA1c change (%) | −0.1 (0.3) | −0.1 (0.2) | ns |
| Pre-treatment HSI | 46.7 (10.9) | 51.9 (9.9) | ns |
| Post-treatment HSI | 44.7 (11.7) | 47.9 (9.2) | ns |
| HSI change | −2.8 (4.9) | −3.2 (4.1) | ns |

Data are presented as median, interquartile range (IQR) for individuals receiving statin therapy versus those not receiving statins. Lipid changes represent absolute differences (post–pre-treatment values).
**Abbreviations:** BMI: body mass index; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; HbA1c: hemoglobin A1c; HSI: hepatic steatosis index; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; P: Mann-Whitney U non-parametric test.

remodeling associated with metabolic dysfunction.[26] This finding is of particular relevance given the accumulating evidence that abnormal peri-organ and intra-organ fat (APIFat) depots—such as MASLD (metabolic dysfunction-associated steatotic liver disease), pericardial, perivascular, and perirenal adipose tissue—play an active pathophysiological role in cardiometabolic risk and vascular disease progression.[27,28] Thus, the pleiotropic metabolic actions of tirzepatide may extend to clinically meaningful reductions in pathogenic fat accumulation beyond the liver, warranting further investigation.

In the present study, a small but significant reduction in eGFR was observed during the initial phase of treatment. This finding is likely attributable to a transient hemodynamic response related to the rapid weight loss induced by tirzepatide rather than to structural renal impairment. Similar early declines in eGFR have been documented with GLP-1 receptor agonists, reflecting reductions in intraglomerular pressure and improved systemic hemodynamics.[29] These initial declines are generally reversible and tend to stabilize over time, ultimately contributing to renal protection.[29,30] The early drop in eGFR may represent a physiological adjustment secondary to reductions in plasma volume, arterial pressure, and obesity-related hyperfiltration, rather than progressive renal injury. As only eGFR was evaluated, the present study cannot provide definitive conclusions regarding clinically meaningful or long-term renal effects. The absence of additional renal markers, such as albuminuria, constitutes a study limitation, since recent meta-analytic data showed a neutral effect of tirzepatide on eGFR, despite a consistent reduction in albuminuria across all dose levels.[31]

Beyond their established effects on metabolic parameters and hepatic steatosis, agents such as tirzepatide may also exert clinically meaningful benefits on vascular risk. MASLD, which frequently coexists with obesity, insulin resistance, and T2DM, is now recognized as an independent contributor to cardiovascular morbidity through shared pathophysiological pathways, including systemic inflammation, endothelial dysfunction, and atherogenic dyslipidemia.[32] Pharmacological strategies targeting these interrelated mechanisms—particularly dual incretin receptor agonists—may therefore confer vascular protection in addition to metabolic improvement.[32,33] Notably, mechanistic evidence from other therapeutic classes, such as statins, has demonstrated modulation of specialized pro-resolving mediators as a potential route toward attenuating vascular inflammation and restoring homeostasis.[34] Taken together, these findings underscore the possibility that tirzepatide may reduce vascular risk through pleiotropic mechanisms beyond glycemic and hepatic endpoints,[32,35] thereby supporting its relevance within the broader cardiometabolic continuum.

The main strength of the present study is that it is the first study conducted in the Greek (i.e., Mediterranean) population, providing real-world data after the approval of tirzepatide. It confirms the beneficial effect of tirzepatide on lipid and glucose metabolism, as well as on liver function in individuals with obesity, but without DM, even at low doses. Importantly, the observed lipid changes occurred regardless of concomitant statin use, suggesting an independent pharmacologic effect of tirzepatide on lipid parameters.

### *4.1. Limitations and strengths of the study*

This study has several limitations. First, the relatively small sample size and short duration of follow-up (12 weeks) may limit the generalizability and long-term interpretability of the findings. Second, the absence of a control group precludes causal inference, and biochemical measurements were performed in different laboratories, potentially introducing inter-assay variability. Third, dietary intake was not systematically recorded, and physical activity was not objectively assessed. Furthermore, subgroup analyses—such as the one comparing statin users versus non-users—should be interpreted with caution, as the number of participants receiving statins was relatively small (n = 18), limiting statistical power.

On the other hand, the study has several strengths. It is the first real-world investigation of tirzepatide in a Mediterranean (Greek) population with obesity but without diabetes, providing novel insights outside the context of randomized controlled trials. The multicenter design enhances external validity, and the prospective assessment of multiple metabolic endpoints—including liver steatosis indices—offers a comprehensive view of the short-term efficacy of tirzepatide in this specific population.

These results add to the growing body of real-world evidence supporting the clinical utility of tirzepatide in the management of obesity beyond the confines of randomized trials.[36]

## 5. Conclusions

In obese adults without diabetes, short-term administration of low-dose tirzepatide was associated with significant reductions in body weight, LDL-C, and triglyceride levels. The effects on HbA1c were statistically significant but clinically modest, and improvements in liver indices were also limited. These findings support the potential role of tirzepatide in the early metabolic management of obesity, even before the onset of overt hyperglycemia. Further long-term studies are needed to confirm these results and determine their sustainability over time.

## CRediT authorship contribution statement

**Nikolaos Angelopoulos:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Sarantis Livadas:** Investigation. **Ioannis Androulakis:** Investigation. **Valentina Petkova:** Investigation. **Andreas Rizoulis:** Investigation. **Anastasios Boniakos:** Investigation. **Rodis Paparodis:** Investigation. **Ploutarchos Tzoulis:** Investigation. **Voula Mentzelopoulou:** Investigation. **Dimos Florakis:** Investigation. **Evangelos Fousteris:** Investigation. **Areti Korakovouni:** Investigation. **Dimitra Zianni:** Investigation. **Zadalla Mouslech:** Investigation. **Manfredi Rizzo:** Writing – review & editing, Supervision. **Dimitri P. Mikhailidis:** Writing – review & editing, Supervision. **Panagiotis Anagnostis:** Supervision, Methodology, Conceptualization.

## Consent for publication

Informed consent was obtained from all participants to this study.

## Ethics approval and consent to participate

The study was approved by the Institutional Research Board (Approval No.: N2024/0121316) of the Hellenic Endocrine Network. Clinical Trials Registry Number: ACTRN12625000071426.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Given his role as Editor-in-Chief of JDC, M.R. had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

All the relevant data are available from the corresponding author upon reasonable request.

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