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Effect of Semaglutide and Tirzepatide on LDL and VLDL Levels in Adults With Type 1 and Type 2 Diabetes: A Comparative Study in Men and Women.

Dr Nageswara Rao T[1], Syed Naseeruddin[2], Aluvala Soujanya[2]
[1]*Associate Professor, Department of Pharmacology, Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram, Andhra Pradesh, India*
[2]*Assistant Professor, Department of Pharmacology, Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram, Andhra Pradesh, India*
[3]*Assistant Professor, Department of Pharmacology, Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram, Andhra Pradesh, India*

Abstract

Background:
Dyslipidemia remains a major cardiovascular risk driver in diabetes, and incretin-based therapies can influence lipoprotein metabolism beyond glucose lowering.

Objectives:
To compare 24-week changes in LDL-C and VLDL-C between semaglutide and tirzepatide, and to evaluate differences by diabetes type and sex.

Methods:
This prospective comparative study was conducted at KIMS & RF, Amalapuram, Andhra Pradesh, India (January–December 2024). One hundred adults with type 1 or type 2 diabetes were allocated to once-weekly semaglutide (n=50) or tirzepatide (n=50) and followed for 24 weeks. Fasting LDL-C and VLDL-C were assessed at baseline and week 24, and changes were compared between groups with stratified analyses by diabetes type and sex.

Results:
The mean age of the participants was 52.6 ± 10.8 years. Men constituted 52.0% and women 48.0% of the study population. Type 2 diabetes was present in 80.0%, while type 1 diabetes was present in 20.0%. Both treatment groups showed significant reductions in lipid levels at 24 weeks. Tirzepatide produced a greater reduction in low-density lipoprotein cholesterol than semaglutide (−30.9 mg/dL vs. −18.5 mg/dL) and a greater reduction in very-low-density lipoprotein cholesterol (−13.3 mg/dL vs. −7.5 mg/dL). Lipid improvement was more marked in type 2 diabetes than in type 1 diabetes. Reductions were observed in both men and women, without a meaningful sex-by-treatment interaction.

Conclusion:
Over 24 weeks, semaglutide and tirzepatide improved LDL-C and VLDL-C in adults with diabetes, with consistently greater lipid lowering observed with tirzepatide across diabetes type and sex strata.

Recommendations:
Tirzepatide may be preferred when lipid risk reduction is a priority in adults with diabetes. Routine lipid monitoring should accompany incretin therapy. Longer, multicenter trials are recommended to confirm durability, cardiovascular outcomes, and safety across diverse diabetic populations.

Keywords: *Semaglutide; Tirzepatide; Low-density lipoprotein cholesterol; Very-low-density lipoprotein cholesterol; Type 1 diabetes; Type 2 diabetes; Incretin therapy; Dyslipidemia.*
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Corresponding author: *Dr. Nageswara Rao T*
Email: *sandeshtokalaoct12@gmail.com*
Associate Professor Department of Pharmacology, Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram, Andhra Pradesh, India

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Introduction

Diabetes mellitus is closely linked to atherosclerotic cardiovascular disease (ASCVD), and dyslipidemia is one of the most consistent contributors to this excess risk. Along with elevated LDL cholesterol (LDL-C), many adults with diabetes have increased triglyceride-rich lipoproteins and VLDL cholesterol (VLDL-C), reflecting insulin resistance, hepatic overproduction of apoB-containing particles, and delayed clearance of remnants. These particles are atherogenic, promote vascular inflammation, and contribute to residual risk even when LDL-C is partially controlled with statins. Contemporary standards therefore emphasize comprehensive ASCVD prevention in diabetes, combining lifestyle therapy, glucose control, and lipid management tailored to overall risk [1].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide durable glycemic improvement and weight loss and, importantly, can improve several lipid parameters. In a systematic review and network meta-analysis, GLP-1RAs were associated with reductions in LDL-C and triglycerides among adults with type 2 diabetes [2]. Mechanistic reviews suggest that GLP-1 signaling can reduce intestinal chylomicron production, modulate hepatic lipid handling, and enhance reverse cholesterol transport [3,4]. Semaglutide has also been shown to improve postprandial lipid metabolism and delay early gastric emptying, which may blunt post-meal excursions of triglyceride-rich lipoproteins [5]. However, the extent of lipid lowering varies across agents and populations, and head-to-head data in routine practice remain limited.

Semaglutide is a once-weekly GLP-1RA with strong evidence for cardiometabolic benefit. In SUSTAIN-6, semaglutide reduced major adverse cardiovascular events in high-risk type 2 diabetes and improved key risk factors [6]. Across the SUSTAIN 1–7 program, semaglutide consistently improved glycemia and body weight with an acceptable safety profile [7]. Real-world observational work has also reported favorable changes in cardiovascular risk markers, including LDL-C, during semaglutide therapy in clinical practice [8]. Because VLDL-C captures remnant cholesterol exposure, demonstrating improvement in both LDL-C and VLDL-C may better reflect atherosclerotic risk modification.

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist that produces marked improvements in glycemia and weight. In SURPASS-2, tirzepatide outperformed semaglutide for glycemic control and body weight reduction in type 2 diabetes [9], and efficacy has been demonstrated in other SURPASS trials across different background therapies [10,11]. Contemporary reviews and a meta-analysis of randomized trials indicate that tirzepatide can also improve lipid parameters, supporting a broader cardiometabolic profile [12,13]. At the same time, incretin-based adjunct therapy in type 1 diabetes remains an emerging area, with recent evidence exploring semaglutide in selected adults with type 1 diabetes and obesity [14]. Therefore, this study compared 24-week changes in LDL-C and VLDL-C between semaglutide and tirzepatide, and evaluated whether responses differed by diabetes type and sex.

Methodology

Study design and setting

This was a prospective, single-center, open-label, comparative, parallel-group study conducted among adults with diabetes who were initiated on once-weekly semaglutide or tirzepatide as part of routine clinical care. The study was carried out at Konaseema Institute of Medical Sciences & Research Foundation (KIMS & RF), Amalapuram, Andhra Pradesh, India, from January to December 2024. KIMS & RF is a tertiary care teaching medical institution that provides outpatient and inpatient clinical services to patients from Amalapuram and the surrounding rural and semi-urban regions of the Konaseema district. The institute has dedicated clinical departments, laboratory facilities, and patient follow-up services, allowing systematic assessment of metabolic and biochemical parameters in patients with diabetes.

Participants and eligibility criteria

Adults aged 18–75 years with physician-diagnosed type 1 diabetes mellitus or type 2 diabetes mellitus were eligible for inclusion if they had fasting low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol values available at baseline and were willing to complete lipid reassessment after 24 weeks of therapy. Participants were required to be on stable background antidiabetic therapy for at least four weeks before enrolment. Lipid-lowering therapy, if already prescribed, was continued without protocol-driven modification during the study period.

Patients were excluded if they were pregnant or lactating, had secondary causes of dyslipidemia such as uncontrolled hypothyroidism or nephrotic syndrome, active liver disease, severe renal impairment with estimated glomerular filtration rate <30 mL/min/1.73 m², recent acute coronary syndrome or stroke within the previous three months, acute infection or hospitalization within four weeks, chronic systemic steroid use, active malignancy, or inability to complete the planned follow-up.

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Study size

A total study size of 100 adults was selected, with 50 participants in the semaglutide group and 50 participants in the tirzepatide group. The study size was arrived at based on the expected availability of eligible patients initiating these therapies during the study period, the feasibility of a 24-week follow-up, and the need for balanced comparison between the two treatment groups. A minimum of approximately 40–45 participants per group was considered adequate to detect a clinically meaningful between-group difference in low-density lipoprotein cholesterol reduction of about 10–12 mg/dL, assuming moderate variability in lipid change, 80% statistical power, and a 5% level of significance. The sample was rounded to 50 participants per group to improve precision and permit subgroup analysis by diabetes type and sex.

Allocation, intervention, and follow-up

Participants were allocated in a 1:1 ratio to semaglutide (n=50) or tirzepatide (n=50) using a clinic-based allocation schedule designed to maintain comparable enrolment between the two groups over time. Both drugs were administered subcutaneously once weekly, with dose escalation based on tolerability and clinician judgment, consistent with routine clinical practice. Background glucose-lowering drugs, lipid-lowering therapy, and antihypertensive treatment were continued and adjusted only when clinically necessary.

All participants received standard advice regarding diet, physical activity, medication adherence, and routine diabetes care at baseline and during follow-up visits. Fasting lipid profile assessment was performed at baseline and repeated at 24 weeks.

Outcomes and measurements

The primary outcomes were absolute changes in low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol from baseline to 24 weeks. Secondary outcomes included percentage change in lipid parameters and subgroup comparisons according to diabetes type and sex. Blood samples were collected after an overnight fast of 8–12 hours at baseline and week 24. Lipid parameters were analyzed in the institutional laboratory using standardized enzymatic methods, and values were recorded in mg/dL.

Bias

Several measures were taken to reduce potential sources of bias. Consecutive eligible patients were enrolled to minimize selection bias. Uniform inclusion and exclusion criteria were applied to both treatment groups. Baseline demographic and lipid characteristics were compared between groups to assess initial comparability. Fasting blood samples were collected using the same protocol at baseline and week 24, and lipid estimation was performed in the institutional laboratory using standardized methods to reduce measurement bias. Standard lifestyle and medication adherence counseling were provided to both groups to limit performance bias. Background lipid-lowering treatment was not changed by protocol, reducing treatment contamination. Statistical adjustment using analysis of covariance was performed for baseline lipid values, diabetes type, age, and sex to control for potential confounding.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median with interquartile range, depending on data distribution. Categorical variables were presented as frequency and percentage. Baseline comparisons between semaglutide and tirzepatide groups were performed using an independent t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Within-group changes from baseline to 24 weeks were assessed using a paired t-test.

Between-group differences in lipid change were analyzed using an independent t-test. Analysis of covariance was performed to adjust for baseline lipid value, diabetes type, age, and sex. Adjusted mean differences were presented with 95% confidence intervals. Subgroup analyses were performed according to diabetes type and sex. A two-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 26.0.

Ethical considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee of Konaseema Institute of Medical Sciences & Research Foundation (KIMS & RF), Amalapuram, Andhra Pradesh, India. The study followed institutional ethical standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment, and only de-identified data were used for analysis to maintain confidentiality.

Results

Participant flow

During the study period, 128 adults with diabetes who were being considered for incretin-based therapy were identified as potentially eligible. Of these, 120 were examined for eligibility, while 8 were not screened further because they were either unwilling to undergo initial assessment or could not complete preliminary clinical evaluation. Among the 120 patients assessed, 20 were excluded. The reasons for

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exclusion were incomplete baseline lipid profile (n=5), unstable background antidiabetic therapy (n=3), secondary causes of dyslipidemia such as uncontrolled hypothyroidism or nephrotic syndrome (n=4), severe renal impairment or active liver disease (n=3), recent acute coronary syndrome or stroke (n=2), and refusal to provide written informed consent (n=3).

Finally, 100 adults were confirmed eligible, enrolled, and included in the study. They were allocated equally into two treatment groups: semaglutide (n=50) and tirzepatide (n=50). All enrolled participants completed the 24-week follow-up and underwent repeat fasting lipid assessment. Therefore, 100 participants were included in the final statistical analysis, with no loss to follow-up.

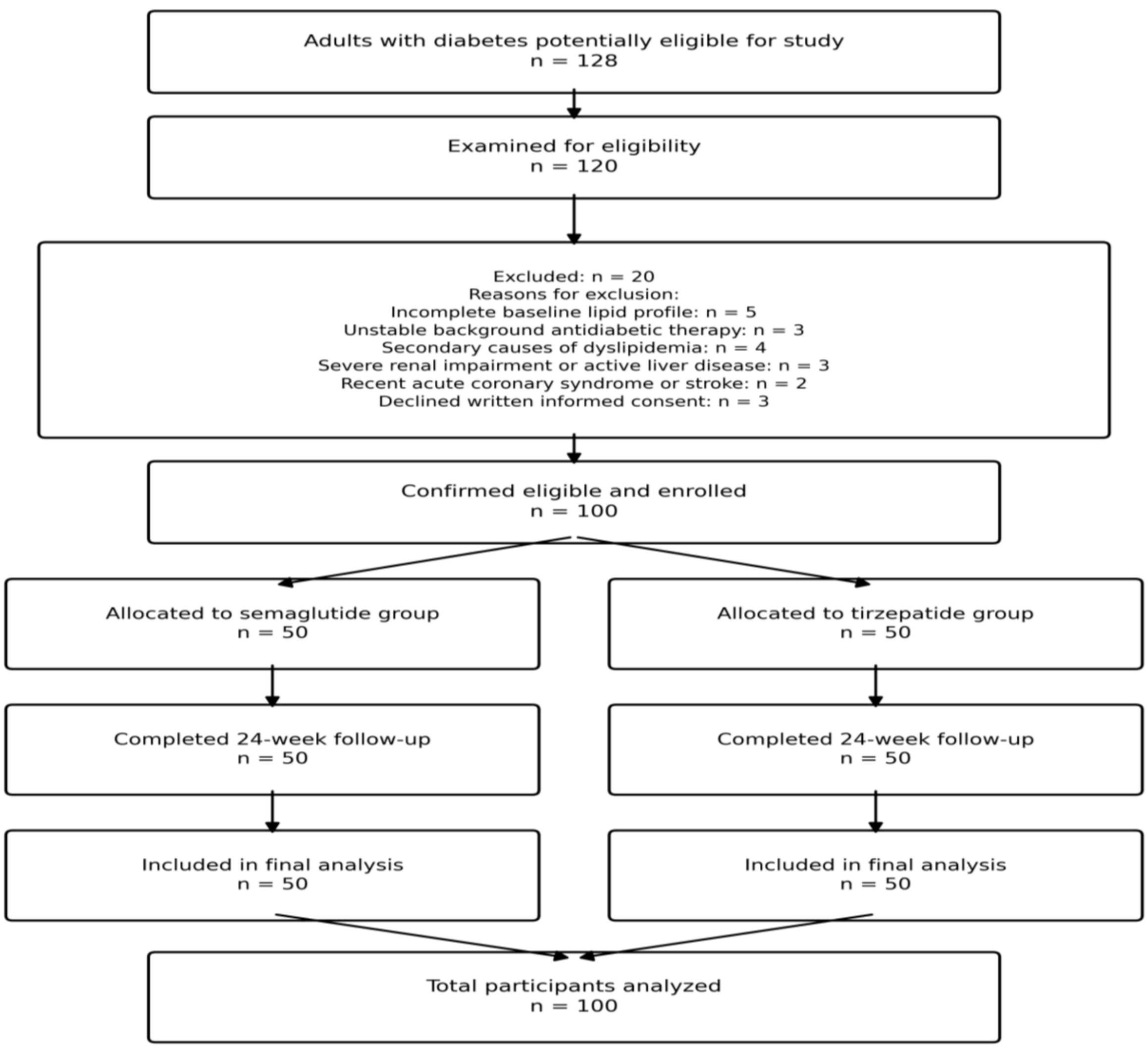

Figure 1: Participant Flow Diagram

A total of 100 adults with diabetes were included and completed lipid follow-up at 24 weeks. The mean age was 52.6 ± 10.8 years (range: 22–74). Type 2 diabetes mellitus constituted 80% (n=80) and type 1 diabetes mellitus 20% (n=20). Overall, 52 participants were men and 48 were women. Participants were allocated to semaglutide (n=50) or tirzepatide (n=50) with comparable baseline lipid profiles and diabetes distribution (Table 1).

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Table 1. Baseline demographic and clinical profile by treatment group (n = 100)

Variable	Semaglutide (n=50)	Tirzepatide (n=50)	p-value
Age (years), mean ± SD	52.3 ± 11.0	52.9 ± 10.6	0.78
Men, n (%)	26 (52.0)	26 (52.0)	1.00
Women, n (%)	24 (48.0)	24 (48.0)	
Diabetes type			0.79
• T1DM, n (%)	9 (18.0)	11 (22.0)	
• T2DM, n (%)	41 (82.0)	39 (78.0)	
Duration of diabetes (years), median (IQR)	7 (4–11)	7 (4–10)	0.66
LDL-C (mg/dL), mean ± SD	122.6 ± 26.4	124.1 ± 27.1	0.76
VLDL-C (mg/dL), mean ± SD	31.8 ± 10.5	32.4 ± 10.8	0.79

At 24 weeks, both groups showed significant reductions in LDL-C and VLDL-C from baseline (paired tests, $p<0.001$ for all). Tirzepatide achieved a lower week-24 LDL-C and a greater mean and percentage LDL-C reduction compared with semaglutide (Table 2). A similar pattern was observed for VLDL-C, where tirzepatide produced lower week-24 values and larger reductions in absolute and percentage terms (Table 2).

Table 2. Change in LDL-C and VLDL-C from baseline to 24 weeks by treatment group (n = 100)

Lipid parameter	Semaglutide (n=50)	Tirzepatide (n=50)	Between-group p-value
LDL-C — Baseline (mg/dL), mean ± SD	122.6 ± 26.4	124.1 ± 27.1	0.76
LDL-C — Week 24 (mg/dL), mean ± SD	104.1 ± 23.7	93.2 ± 21.8	0.02
LDL-C — Mean change (Δ), mean ± SD	−18.5 ± 14.2	−30.9 ± 15.6	<0.001
LDL-C — % change, mean ± SD	−14.8 ± 10.9	−24.7 ± 11.8	<0.001
VLDL-C — Baseline (mg/dL), mean ± SD	31.8 ± 10.5	32.4 ± 10.8	0.79
VLDL-C — Week 24 (mg/dL), mean ± SD	24.3 ± 8.9	19.1 ± 7.6	0.003
VLDL-C — Mean change (Δ), mean ± SD	−7.5 ± 6.3	−13.3 ± 7.1	<0.001
VLDL-C — % change, mean ± SD	−22.9 ± 17.4	−39.8 ± 18.6	<0.001

When stratified by diabetes type, the magnitude of lipid improvement was larger in T2DM than T1DM in both arms, though tirzepatide remained superior within each diabetes subgroup for both LDL-C and VLDL-C changes (Table 3).

Table 3. Mean change in LDL-C and VLDL-C at 24 weeks stratified by diabetes type (n = 100)

Diabetes type	Treatment	n	ΔLDL-C (mg/dL), mean ± SD	p (between groups)	ΔVLDL-C (mg/dL), mean ± SD	p (between groups)
T1DM	Semaglutide	9	−12.4 ± 11.8	0.04	−5.3 ± 4.7	0.03
	Tirzepatide	11	−22.1 ± 12.6		−9.6 ± 5.2	
T2DM	Semaglutide	41	−19.8 ± 14.5	<0.001	−8.0 ± 6.5	<0.001
	Tirzepatide	39	−33.4 ± 15.6		−14.4 ± 7.2	

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Sex-stratified analysis showed reductions in men and women in both arms. Women exhibited slightly larger reductions within each arm, but between-sex differences were not statistically significant after adjustment. Between-group comparisons continued to favor tirzepatide for both LDL-C and VLDL-C (Table 4).

Table 4. Mean change in LDL-C and VLDL-C at 24 weeks stratified by sex (n = 100)

Sex	Treatment	n	ΔLDL-C (mg/dL), mean ± SD	p (between groups)	ΔVLDL-C (mg/dL), mean ± SD	p (between groups)
Men	Semaglutide	26	−17.1 ± 13.8	<0.001	−7.0 ± 6.1	<0.001
	Tirzepatide	26	−29.6 ± 15.1		−12.6 ± 6.9	
Women	Semaglutide	24	−20.0 ± 14.7	<0.001	−8.0 ± 6.6	<0.001
	Tirzepatide	24	−32.3 ± 16.2		−14.1 ± 7.4	

Adjusted ANCOVA models controlling for baseline lipid values, diabetes type, age, and sex confirmed that tirzepatide was independently associated with larger LDL-C reduction (adjusted mean difference: −11.6 mg/dL; 95% CI: −17.2 to −6.0; p<0.001) and larger VLDL-C reduction (adjusted mean difference: −5.4 mg/dL; 95% CI: −8.1 to −2.7; p<0.001). No significant treatment×sex interaction was observed (p=0.28 for LDL-C; p=0.34 for VLDL-C).

Discussion

The present study demonstrated that both semaglutide and tirzepatide significantly reduced low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol over 24 weeks in adults with diabetes. The primary support for this finding comes from the within-group lipid changes observed between baseline and week 24, where both treatment arms showed statistically significant reductions in low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol. Semaglutide reduced low-density lipoprotein cholesterol by −18.5 ± 14.2 mg/dL and very-low-density lipoprotein cholesterol by −7.5 ± 6.3 mg/dL, whereas tirzepatide produced larger reductions of −30.9 ± 15.6 mg/dL and −13.3 ± 7.1 mg/dL, respectively. The between-group differences were statistically significant for both lipid parameters, and adjusted analysis confirmed that tirzepatide was independently associated with greater lipid reduction after controlling for baseline lipid values, diabetes type, age, and sex. This indicates that the observed benefit was not merely due to baseline group differences but was more likely related to the treatment effect itself.

These findings suggest that incretin-based therapies may contribute to cardiovascular risk reduction through mechanisms extending beyond glucose control. The simultaneous reduction in low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol is clinically relevant because both lipid fractions contribute to atherogenic particle burden in patients with diabetes. The larger reduction observed with tirzepatide may reflect the broader metabolic effect of dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonism. Improved insulin sensitivity, reduced body weight, decreased hepatic very-low-density lipoprotein production, and enhanced clearance of triglyceride-rich particles may together explain the stronger lipid-lowering pattern seen with tirzepatide.

After this interpretation, the findings can be compared with existing evidence. The greater cardiometabolic effect of tirzepatide is consistent with randomized evidence from SURPASS-2, where tirzepatide showed superior metabolic efficacy compared with semaglutide in patients with type 2 diabetes [9]. Sustained efficacy across other SURPASS trials also supports the broader metabolic benefit of tirzepatide [10,11]. Reviews and trial syntheses have similarly reported favorable effects of tirzepatide on lipid parameters across different doses and clinical settings [12,13]. In comparison, semaglutide also has well-established cardiometabolic benefits, as demonstrated in SUSTAIN-6 and the wider SUSTAIN clinical program [6,7]. Real-world evidence has further shown that semaglutide improves several cardiovascular risk markers in patients with type 2 diabetes [8]. Therefore, the present findings align with the existing literature while adding comparative data on low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol changes in a routine tertiary care cohort.

The biological plausibility of the observed lipid reduction is supported by known incretin-mediated effects on lipid metabolism. Glucagon-like peptide-1 signaling can reduce intestinal lipoprotein production, improve hepatic lipid handling, and influence reverse cholesterol transport, thereby reducing circulating atherogenic lipoproteins [3,4]. Semaglutide has also been shown to improve postprandial glucose and lipid metabolism and delay early gastric emptying, which may reduce post-meal exposure to triglyceride-rich lipoproteins and their remnants [5]. Tirzepatide, through dual glucose-dependent insulinotropic

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polypeptide and glucagon-like peptide-1 receptor activation, may exert a stronger effect on body weight, insulin sensitivity, hepatic lipid metabolism, and lipoprotein clearance. This may explain why tirzepatide produced larger reductions than semaglutide in the present study.

Subgroup findings also require interpretation. Lipid improvement was greater in participants with type 2 diabetes than in those with type 1 diabetes. This pattern is biologically reasonable because type 2 diabetes is more strongly associated with insulin resistance, hepatic overproduction of very-low-density lipoprotein particles, hypertriglyceridemia, and remnant cholesterol accumulation. Therefore, therapies that improve insulin sensitivity and reduce adiposity may produce more visible lipid changes in type 2 diabetes. However, tirzepatide remained superior within both diabetes subgroups, suggesting that its lipid-lowering effect was not limited to type 2 diabetes alone. The study also observed lipid reductions in both men and women, with no clinically meaningful sex-by-treatment interaction. This suggests that the comparative lipid benefit of tirzepatide was broadly similar across sex groups.

The findings should also be interpreted in the context of current diabetes care. Very-low-density lipoprotein cholesterol can serve as a practical marker of triglyceride-rich remnant lipoprotein burden, which contributes to residual cardiovascular risk in diabetes. Current standards emphasize comprehensive cardiovascular risk reduction in diabetes, including lipid control, glycemic management, weight reduction, and individualized pharmacotherapy. In this setting, incretin-based therapies that improve glycemic status and reduce atherogenic lipid fractions may provide added value alongside statin-based lipid management. Nevertheless, the present study did not assess apolipoprotein B, triglyceride subfractions, statin intensity, body weight change, or cardiovascular outcomes. Hence, the lipid changes should be interpreted as intermediate biochemical improvements rather than direct evidence of cardiovascular event reduction.

Overall, the study findings indicate that semaglutide and tirzepatide both improve atherogenic lipid parameters over 24 weeks in adults with diabetes, with tirzepatide producing a consistently greater reduction in low-density lipoprotein cholesterol and very-low-density lipoprotein cholesterol. The results are biologically plausible, supported by adjusted within-study analysis, and consistent with previous clinical trial and review evidence. Larger multicenter studies with longer follow-up, detailed lipid phenotyping, body weight assessment, statin-stratified analysis, and cardiovascular outcome evaluation are required to confirm the durability and clinical significance of these findings.

Generalizability

The findings are generalizable to adult patients with type 1 and type 2 diabetes receiving incretin-based therapy in tertiary care settings. However, extrapolation to pediatric populations, elderly patients with advanced comorbidities, or non-Indian populations should be made cautiously and validated through larger, multicenter studies.

Conclusion

In adults with type 1 and type 2 diabetes at a tertiary care center, once-weekly semaglutide and tirzepatide produced significant reductions in LDL-C and VLDL-C over 24 weeks. Tirzepatide achieved lower week-24 LDL-C and VLDL-C values and larger absolute and percentage reductions than semaglutide. This advantage persisted after adjustment for baseline lipid levels, diabetes type, age, and sex, and no meaningful treatment-by-sex interaction was detected. Lipid improvements were larger in type 2 than type 1 diabetes, yet tirzepatide remained superior within both subgroups. These findings support tirzepatide when additional atherogenic lipid improvement is prioritized in routine diabetes care. Multicenter studies should confirm durability and link lipid changes to cardiovascular outcomes.

Limitations

This single-center study had a modest sample size and a 24-week follow-up, limiting assessment of long-term lipid durability and cardiovascular outcomes. Allocation was clinic-based and unblinded, so residual confounding and adherence variation can influence effect estimates. ApoB, triglycerides, and lipoprotein subfractions were not analyzed, and background statin intensity was not stratified, restricting mechanistic interpretation and generalizability across populations and care models.

Recommendations

Clinicians should consider incretin-based therapies as part of comprehensive cardiovascular risk management in adults with diabetes, particularly in patients with coexisting dyslipidemia. Tirzepatide may be favored when greater LDL-C and VLDL-C reduction is desired, while semaglutide remains an effective alternative. Regular lipid profiling should be integrated into follow-up protocols to assess therapeutic response. Treatment choice should be individualized based on diabetes type, metabolic profile, tolerability, and patient preference. Future studies should focus on long-term lipid sustainability, hard cardiovascular outcomes, cost-effectiveness, and real-world applicability across diverse healthcare settings.

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Abbreviations
LDL-C low-density lipoprotein cholesterol,
VLDL-C very-low-density lipoprotein cholesterol,
T1DM type 1 diabetes mellitus,
T2DM type 2 diabetes mellitus,
KIMS & RF Konaseema Institute of Medical Sciences and Research Foundation,
GLP-1 glucagon-like peptide-1,
GIP glucose-dependent insulinotropic polypeptide.

Source of funding
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Conflict of interest
The author declares no conflict of interest.

Author contributions
NT-Concept and design of the study, results interpretation, review of literature, and preparation of the first draft of the manuscript. Statistical analysis and interpretation, revision of manuscript. **SN**-Concept and design of the study, results interpretation, review of literature, preparing the first draft of the manuscript, and revision of the manuscript.**AS**-Review of literature and preparing the first draft of the manuscript. Statistical analysis and interpretation.

Data availability
Data available on request

Author Biography
Dr. T. Nageswararao is currently serving as an Associate Professor of Pharmacology at Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram, East Godavari District, Andhra Pradesh, India. He holds a doctoral degree in Medical Pharmacology from the prestigious Index Medical College and Research Institute, Madhya Pradesh. With over 16 years of teaching experience in various medical institutions, Dr. Nageswararao has made significant contributions to the field of pharmacology. His academic work includes nine research publications in reputed national and international journals, including one article indexed in PubMed. His dedication to research and education continues to enrich the academic and clinical landscape of medical pharmacology.**T.Nageswararao**:https://orcid.org/0009-0005-1638-6897

Syed Naseeruddin is an Assistant Professor in the Department of Pharmacology at Konaseema Institute of Medical Sciences and Research Foundation (KIMS & RF), Amalapuram, Andhra Pradesh, India. He is actively involved in undergraduate medical teaching and clinical pharmacology training. His academic interests include rational drug use, pharmacovigilance, and metabolic disorder therapeutics. He has contributed to institutional research activities and is engaged in guiding student research projects.

Aluvala Soujanya is an Assistant Professor in the Department of Pharmacology at Konaseema Institute of Medical Sciences and Research Foundation (KIMS & RF), Amalapuram, Andhra Pradesh, India. She is dedicated to teaching pharmacology to undergraduate medical students and has a keen interest in diabetes pharmacotherapy, adverse drug reaction monitoring, and clinical research. She actively participates in academic, research, and curricular development activities within the department.

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