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SEMAGLUTIDE VERSUS INSULIN GLARGINE IN TYPE 2 DIABETES WITH FATTY LIVER DISEASE

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ABSTRACT

Objective: To compare the effects of semaglutide and insulin glargine on glycaemic control, body weight, and liver enzymes in patients with type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) following secondary failure to oral hypoglycemic agents (OHA).

Methods: A 12-weekrandomized comparative study was conducted at Islamabad, Pakistan. Adults aged 30–65 years with T2DM, MASLD, and secondary OHA failure were randomized to semaglutide once weekly (Group 1, n=60) or subcutaneous insulin glargine once daily (Group 2, n=60) for 12 weeks. Outcomes parameters included HbA1c, body weight, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and adverse effects, assessed at baseline and week 12. Within-group and between-group comparisons used paired and independent sample t-tests ($p \leq 0.05$).

Results: Both therapies showed significant improvements in HbA1c, AST, and ALT. Semaglutide produced greater reductions in HbA1c (10.82±0.70% to 9.84±0.64%), body weight (94.91±6.47 to 89.55±6.00 kg), AST (46.09±3.01 to 40.32±2.99 U/L), and ALT (82.16±15.72 to 71.15±15.61 U/L) compared with insulin glargine, which produced modest glycemic and hepatic improvement but was associated with weight gain. Between-group comparisons at week 12 favored semaglutide for all primary outcomes. Mild gastrointestinal effects were more frequent with semaglutide; weight gain, hypoglycemia, and injection-site reactions were observed with insulin glargine. No serious adverse events or treatment discontinuations occurred.

Conclusion: Semaglutide demonstrated superior glycaemic, weight, and hepatic outcomes as compared to insulin glargine in T2DM patients with MASLD following secondary OHA failure, with a favorable safety profile over 12 weeks.

KEYWORDS: GLP-1 receptor agonists;Semaglutide; Insulin glargine; Type 2 diabetes mellitus; metabolic dysfunction-associated steatotic liver disease.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder described by insulin resistance, impaired beta-cell function, and persistent hyperglycemia. It is a major contributor to global morbidity and mortality and is closely associated with cardiovascular, renal, neurologic, and hepatic complications. The burden of type 2 diabetes is particularly high in South Asian populations, and Pakistan has been reported among the countries with the highest diabetes burden globally (1).

Among the extra-pancreatic manifestations of type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD) has gained increasing clinical relevance. MASLD is recognized as one of the most common chronic liver diseases worldwide and is highly prevalent in patients with T2DM(2,3). In T2DM patients, MASLD is associated not only with abnormal liver enzymes and progressive hepatic injury but also with increased cardiovascular and metabolic risk (4).

Treatment intensification after secondary failure to oral hypoglycemic agents (OHA) remains a common clinical challenge. Insulin therapy is effective in lowering blood glucose, but it is often accompanied by weight gain and hypoglycemia (5,6). By contrast, glucagon-like peptide-1 (GLP-1) receptor analogues improve glucose-dependent insulin secretion, control glucagon release, slow down gastric emptyingand reduce appetite, thereby producing both glycemic and weight-related benefits(5). These pleiotropic actions have made GLP-1 receptor analogue therapy an

increasingly attractive option in T2DM patients who also have obesity-related and liver-related metabolic complications(3,7).

The new trends exhibits that GLP-1 receptor agonist therapy may also recover hepatic steatosis and abnormalities in liver enzyme in patients with MASLD (8). Furthermore, semaglutide and liraglutide demonstrates important cardio-metabolic benefits in large clinical trials, supporting the broader therapeutic value of this drug class in type 2 diabetes (6). Recent research has also shown that semaglutide reduces cardiovascular risk in overweight and obese people even when they do not have diabetes, which supports the therapeutic class's wider cardiometabolic relevance(9). However, the data against insulin comparison therapy remains limited, specifically in regional and local populations. Moreover, most of the previous literature focused alone either on glycemic endpoints or on broader metabolic effects without simultaneously examining liver-related biochemical response, weight change, and treatment tolerability in the same cohort.

2. MATERIALS AND METHODS

This randomized comparative trial was conducted at the Department of Pharmacology and Therapeutics, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, in collaboration with the Medical Unit, Pakistan Institute of Medical Sciences, Islamabad. Before the start of the study, approval was obtained from the institutional ethical review board (Approval No. 1450) and the Advanced Studies & Research Board (Approval No. 2025-2130). Patients were enrolled between September and December 2025 and were subsequently monitored for the duration of their 12-week treatment course. Written informed consent was obtained from each participant prior to enrollment.

Adult patients aged 30 to 65 years of either sex with established T2DM, MASLD, and secondary failure to OHA were eligible for inclusion. Secondary failure to oral therapy was defined clinically as inadequate glycemic control despite prior oral antidiabetic treatment, necessitating intensification to injectable therapy. Patients were excluded if they had type 1 diabetes mellitus; were pregnant or lactating; had a history of pancreatitis or medullary thyroid carcinoma; had severe renal impairment with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2; had known hypersensitivity to GLP-1 receptor analogues or insulin; or had active gastrointestinal disease or severe gastroparesis.

Patients presenting to the outpatient department of the Pakistan Institute of Medical Sciences were screened on a daily basis for eligibility. Those who fulfilled the predefined inclusion and exclusion criteria were enrolled and subsequently allocated to one of the two treatment groups using simple randomization, performed after confirmation of eligibility and before treatment initiation. Participant screening, randomization, follow-up, and inclusion in the per-protocol analysis are illustrated in the CONSORT diagram (Figure 1).

Eligible participants were assigned to one of two treatment groups. Patients in Group 1 received semaglutide administered subcutaneously once weekly, initiated at a dose of 0.5 mg once weekly. Dose escalation followed a uniform protocol-driven schedule according to clinical requirement, with escalation at each 4-week interval; by week 12, 20% of patients were receiving 1.5 mg once weekly and 80% were receiving 2 mg once weekly. Patients in Group 2 received insulin glargine administered once daily by subcutaneous injection, with the initial dose calculated as body weight in kilograms multiplied by 0.5 units per day and subsequently titrated according to glycemic response and clinical assessment. No oral antidiabetic therapy was continued after enrollment in either group.

Baseline evaluation included demographic profile, comorbidity assessment, duration of diabetes, baseline ultrasonographic (USG) evidence of fatty liver disease, glycated hemoglobin, body weight, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Follow-up evaluation was performed after completion of 12 weeks of therapy and included reassessment of glycated hemoglobin, body weight, AST, ALT, and treatment-emergent adverse effects. Baseline USG grading was used to document the presence and severity of MASLD at study entry, and post-treatment hepatic response was assessed biochemically using AST and ALT values. The primary objective was to compare the effects of GLP-1 receptor analogue therapy and insulin therapy in patients with T2DM and MASLD, with measured endpoints comprising change in glycated hemoglobin, change in body weight, change in AST, change in ALT, and the incidence and pattern of adverse effects over 12 weeks. Patients were monitored for adverse effects throughout the treatment period; those in the semaglutide group experienced constipation, nausea, diarrhea, and vomiting, while those in the insulin group experienced weight gain, symptomatic hypoglycemia, and injection-site reactions. All adverse effects were mild, and none resulted in treatment discontinuation or a serious adverse event.

Statistical analysis was performed using SPSS version 27.0. Qualitative variables were summarized as frequency and percentage, and quantitative variables were presented as mean ± standard deviation. Within-group changes from baseline to week 12 were compared using the paired sample t-test, and continuous variables between the two treatment groups were compared using the independent sample t-test. The chi-square test was used to assess categorical variables, and statistical significance was defined as a p-value of 0.05 or lower(10).

3. RESULTS

Total120 patients were included in the final analysis by considering 60 patients in each treatment group. The clinical and baseline demographiccharacteristics are shown in Table 1. Group 1 consist of significantly higher proportion of males, whereas Group 2 consist of higher proportion of females with statistically significant of ($p = 0.028$). In contrast, majority of patients in both groups had Grade II disease on baseline ultrasonography, and a significant percentage had associated comorbidities; however, age, duration of type 2 diabetes mellitus, baseline USG grade, comorbidity status, dyslipidaemia, and hypertension did not differ significantly between the two groups, indicating overall comparability for these baseline characteristics aside from sex distribution.

During the 12-week treatment period adverse effects observed aredescribed below. Any adverse effect was reported in 73% of patients in Group 1 compared with 37% in Group 2. Gastrointestinal adverse effects were observed only in the semaglutide group, with nausea reported in 40% of patients, diarrhea in 13%, vomiting in 13%, and constipation in 7%. In contrast, weight gain, symptomatic hypoglycemia, and injection site reaction were observed only in the insulin glargine group, occurring in 20%, 8%, and 8% of patients, respectively. All adverse effects were mild, and no serious adverse event or treatment discontinuation occurred during follow-up.

Within-group changes from baseline to week 12 are as follows. In Group 1, HbA1c decreased from 10.82 ± 0.70 to 9.84 ± 0.64, representing a 9.06% reduction. Body weight also declined from 94.91 ± 6.47 kg to 89.55 ± 6.00 kg, corresponding to a 5.65% reduction. Similarly, AST decreased from 46.09 ± 3.01 U/L to 40.32 ± 2.99 U/L, and ALT decreased from 82.16 ± 15.72 U/L to 71.15 ± 15.61 U/L, corresponding to reductions of 12.52% and 13.40%, respectively. All within-group changes were statistically significant ($p < 0.001$) in Group 1.

In Group 2, HbA1c also decreased significantly from 10.68 ± 0.70 to 10.20 ± 0.75, corresponding to a 4.49% reduction. AST and ALT likewise showed significant but smaller declines, from 45.78 ± 2.80 U/L to 43.83 ± 2.82 U/L and from 84.73 ± 15.87 U/L to 82.17 ± 15.88 U/L, respectively. In contrast to Group 1, body weight increased significantly from 74.09 ± 5.35 kg to 75.77 ± 6.04 kg, corresponding to a 2.27% increase. All within-group changes in Group 2 were also statistically significant ($p < 0.001$).

Between-group comparisons at baseline and week 12 are as follows. At baseline, there were no statistically significant differences among the groups in HbA1c ($p = 0.286$), AST ($p = 0.558$), or ALT ($p = 0.375$). At week 12, however, significant between-group variations were observed in favor of Group 1 for HbA1c ($p = 0.005$), AST ($p < 0.001$), and ALT ($p < 0.001$). Body weight differed significantly between the two groups at baseline and remained significantly different at week 12 ($p < 0.001$ at both time points); therefore, between-group interpretation for body weight should be made cautiously and considered alongside within-group change. Overall, the direction of treatment effect across key study outcomes favored semaglutide.

To account for baseline differences, analysis of covariance was performed for week-12 outcomes using the corresponding baseline value as a covariate. The adjusted analysis confirmed a significant between-group difference in favour of Group 1 for all four outcomes shown in Table 2. After adjustment, the mean week-12 HbA1c was lower in Group 1 compared to Group 2 (adjusted mean difference: -0.49, 95% CI: -0.58 to -0.40; $p < 0.001$). Similarly, adjusted week-12 body weight remained lower in Group 1 (adjusted mean difference: -5.37 kg, 95% CI: -7.25 to -3.49; $p < 0.001$). Group 1 also showed significantly lower adjusted AST (adjusted mean difference: -3.74 U/L, 95% CI: -4.46 to -3.03; $p < 0.001$) and ALT (adjusted mean difference: -8.52 U/L, 95% CI: -9.73 to -7.30; $p < 0.001$) values at week 12 compared with Group 2. These adjusted findings were consistent with the unadjusted analyses and further supported the overall superiority of semaglutide across glycaemic, anthropometric, and liver-related biochemical outcomes.

Table 1: Baseline demographic and clinical data of patients in semaglutide and insulin glargine groups

Variables	Group 1 (n = 60)	Group 2 (n = 60)	p-value
Female, n (%)	23 (38%)	35 (58%)	0.028
Male, n (%)	37 (62%)	25 (42%)	
Age, years, mean ± SD	56.65 ± 5.14	56.62 ± 4.58	0.970
Duration of T2DM, years, mean ± SD	8.00 ± 2.06	8.45 ± 2.35	0.267
USG Grade I, n (%)	23 (38%)	20 (33%)	0.568
USG Grade II, n (%)	37 (62%)	40 (67%)	
No comorbidity, n (%)	20 (33%)	14 (23%)	0.224
Comorbidity present, n (%)	40 (67%)	46 (77%)	
Dyslipidemia, n (%)	25 (42%)	28 (47%)	0.581
Hypertension, n (%)	28 (47%)	33 (55%)	0.361

***Note:** Group 1 represents the semaglutide group, and Group 2 represents the insulin glargine group. The chi-square test was performed to determine p-values for categorical variables, whereas p-values for age and duration of T2DM were determined using independent samples t-test.*

Table 2: Adjusted between-group comparison of week-12 outcomes using ANCOVA

Outcomes	Adjusted mean Group 1	Adjusted mean Group 2	Adjusted mean difference	95% CI	p-value
HbA1c	9.77	10.27	-0.493	-0.58 to -0.40	<0.001
Body weight	79.97	85.34	-5.37	-7.25 to -3.49	<0.001
AST (U/L)	40.21	43.95	-3.74	-4.46 to -3.03	<0.001
ALT (U/L)	72.40	80.92	-8.52	-9.73 to -7.30	<0.001

***Note:** Adjusted means were calculated using ANCOVA with the corresponding baseline value included as a covariate.*

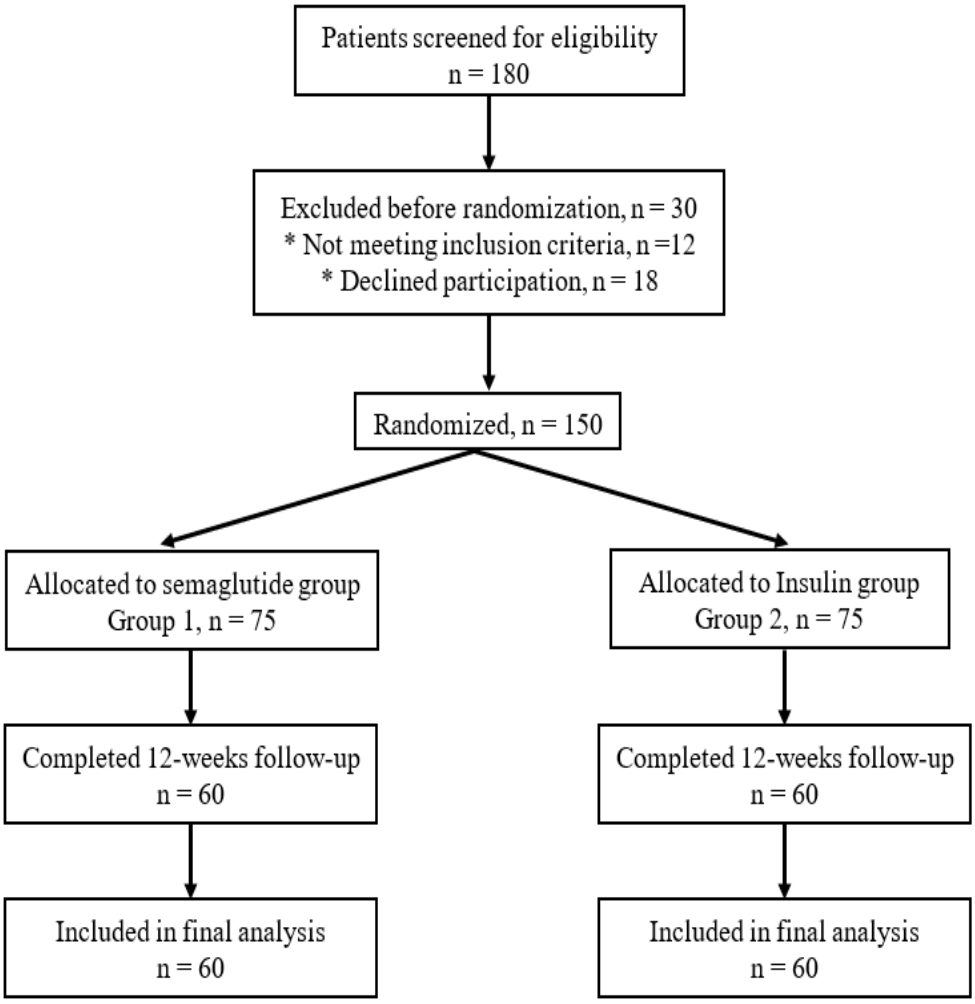


Figure 1. CONSORT diagram showing participant screening, randomization, follow-up, and inclusion in the per-protocol analysis

4. DISCUSSION

This study compared the effects of semaglutide and insulin glargine in patients having T2DM with MASLD and failure to OHA therapy. Semaglutide consistently outperformed insulin glargine across glycemic, anthropometric, and hepatic biochemical parameters over the 12-week follow-up. Insulin glargine, by contrast, yielded more modest HbA1c reductions and was accompanied by weight gain with little improvement in liver enzymes. Importantly, these between-group differences persisted after ANCOVA adjustment for baseline values, which rules out the possibility that observed effects simply reflected pre-existing group differences rather than true treatment responses. The

findings are biologically plausible and are broadly consistent with the known cardiometabolic profile of GLP-1 receptor agonists reported previously(3,5–7).

Body weight exhibited a divergent response to two treatments, representing one of the most clinically significant observations from this study. Semaglutide group patients showed significant reduction in body weight, but insulin glargine recipient patients showed increase in body weight as compared to baseline values. Since excess adiposity and insulin resistance are central to the pathophysiology of both T2DM and MASLD, this difference is highly relevant. Insulin resistance is considered a major pathogenic factor in MASLD progression which influences hepatic lipogenesis and metabolic dysfunction. This factor strengthens the biological importance of weight reduction in this setting (11). Although baseline body weight differed significantly between groups, the adjusted ANCOVA analysis still showed a significant difference in favor of semaglutide in week 12 results. ANCOVA results support that the observed body-weight effect was not merely a consequence of baseline imbalance. From a clinical perspective, this is important because treatment intensification in patients with coexisting T2DM and MASLD should ideally improve glycemic control without exacerbating weight-related metabolic burden.

The liver enzyme results further support a beneficial hepatic biochemical effect with semaglutide. Both AST and ALT declined significantly in both groups, but the magnitude of reduction was more in semaglutide group. These findings are clinically relevant because MASLD and T2DM are closely linked through shared mechanisms such as insulin resistance, obesity, and broader metabolic dysfunction, and progression of MASLD in patients with diabetes is associated with increased hepatic as well as extrahepatic risk (2,4). In this study, AST and ALT were comparable among both groups at baseline and were significantly lower in the semaglutide group at week 12. The results remained significantly different after adjustment for baseline values. This suggests that semaglutide providessignificant improvement in liver-related biochemical status in patients with MASLD and T2DM than insulin glargine over short-term follow-up. Nevertheless, this interpretation should remain appropriately cautious. MASLD in the present study was documented at baseline by ultrasonography, but follow-up ultrasonographic grading was not performed. Therefore, the study demonstrates improvement in liver enzyme markers in a cohort with MASLD rather than direct imaging-confirmed regression of hepatic steatosis.

The safety profile observed in this study is consistent with previously reported pharmacologic behavior of these two therapies. Semaglutide recipient patients faced Gastrointestinal adverse effects including nausea, diarrhea, vomiting, and constipation. Whereas insulin group demonstrated adverse effects such as weight gain, symptomatic hypoglycemia, and injection-site reaction. Overall, all adverse effects were mild, and therapy continued till the completion of study period. These findings suggest that although semaglutide was associated with a higher overall frequency of treatment-emergent adverse effects, its tolerability remained acceptable in this study population, especially when weighed against its superior glycemic, anthropometric, and hepatic biochemical benefits.

This study has multiple strengths compared to few limitations as per the statistical results. It compares two commonly used injectable treatment therapies in T2DM having MASLD and secondary failure to OHA. Multiple outcomes including glycemic control, body weight, liver-related biochemical response, and adverse effects were measured in this study. Moreover, ANCOVA-based adjusted analysis strengthens the interpretation of 12 week results as compared to baseline values of all studied variables. There are few limitations of this study which needs consideration before the final application of these results. The effect on MASLD was observed indirectly through ALT and AST rather than follow-up USG grading due to limited resources. Baseline gender distribution and body weight differed significantly between two groups which introduces some imbalance in groups comparability. Follow-up period was limited to 12 weeks, which restricts inference regarding the long-term durability of the observed treatment effects. Lastly, the study was conducted in a relatively modest sample size at a single-center clinical setting, which may limit generalizability.

Overall, the results of this study clearly highlight that semaglutide is more favorable option for improvement in glycemic control, weight, and liver-related biochemical parameters in patients with T2DM and MASLD after secondary failure to OHA. The gastrointestinal side effects associated with semaglutide are real and these should be informed to the patients before the start of treatment. These side effects were mild and self-limiting and did not diminish the drug's overall benefit. The consistency of the results across both unadjusted and adjusted analyses adds further support to this interpretation.

5. CONCLUSION

Among patients of T2DM and MASLD who had not adequately responded to OHA, semaglutide outperformed insulin glargine over 12 weeks in HbA1c, body weight, AST, and ALT. The advantage persisted in conventional comparative analyses as well as baseline-adjusted ANCOVA models which supports the robustness of overall treatment effect. Gastrointestinal side effects were more frequent with semaglutide, but these events were mild and did not lead to treatment discontinuation. Whereas insulin glargine side effects included weight gain, symptomatic hypoglycemia, and injection-site reaction. Based on theseresults, semaglutide appears to offer a more favorable metabolic and hepatic biochemical profile than insulin glargine in this patient population.

REFERENCES

1. Basit A, Waris N, Fawwad A, Tahir B, Siddiqui IA, Abro MUR, et al. Glycemic status and general characteristics among individuals with undiagnosed diabetes; findings from second National Diabetes Survey of Pakistan 2016–2017 (NDSP 08). Diabetes Metab Syndr Clin Res Rev. 2022 Jun;16(6):102535.
2. Cusi K, Abdelmalek MF, Apovian CM, Balapattabi K, Bannuru RR, Barb D, et al. Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the American Diabetes Association. Diabetes Care. 2025 Jul 1;48(7):1057–82.
3. Mollace R, Longo S, Nardin M, Tavernese A, Musolino V, Cardamone A, et al. Role of MASLD in CVD: A review of emerging treatment options. Diabetes Res Clin Pract. 2024 Nov;217:111891.
4. Chouik Y, Canivet CM, Julla JB, Mouillot T, Parlati L, Rouland A, et al. Management of patients with type 2 diabetes and MASLD: An overview and joint statement. Diabetes Metab. 2025 Nov;51(6):101709.
5. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834–44.
6. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311–22.
7. Chrysavgis L, Mourelatou NG, Cholongitas E. Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs): A Pan-Steatotic Liver Disease Treatment? Biomedicines. 2025 Jun 20;13(7):1516.
8. Tamilwanan S, Aziz Z, Rong LY, Bitar AN, Zarzour RH Al, Alshehade SA. Efficacy of GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists in managing MALFD: a meta-analysis of randomized controlled trials. BMC Gastroenterol. 2025 Oct 27;25(1):765.
9. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023 Dec 14;389(24):2221–32.
10. Malik AA, Wani MA, Bashir S, Ahrar N, Khurshid MS, Kangoo A, et al. Single-layer vs Double-layer Intestinal Anastomosis: A Prospective Comparative Study. Euroasian J hepato-gastroenterology. 2025 Jun 18;15(1):18–23.
11. Bo T, Gao L, Yao Z, Shao S, Wang X, Proud CG, et al. Hepatic selective insulin resistance at the intersection of insulin signaling and metabolic dysfunction-associated steatotic liver disease. Cell Metab. 2024 May;36(5):947–68.