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ORIGINAL ARTICLE

Comparative Efficacy of Resmetirom, GLP-1 Receptor Agonists, and Pioglitazone for Fibrosis Regression and MASH Resolution in Metabolic Dysfunction-Associated Steatohepatitis: A Systematic Review and Narrative Synthesis of Network Meta-Analyses with Implications for Pakistan

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent a rapidly growing public health challenge in Pakistan and South Asia due to rising prevalence of obesity, type 2 diabetes, and metabolic syndrome. Pharmacological options beyond lifestyle modification are essential for patients with moderate-to-advanced fibrosis (F2–F3). This systematic review synthesizes comparative efficacy data on resmetirom (thyroid hormone receptor-β agonist), GLP-1 receptor agonists (e.g., semaglutide), and pioglitazone for key histological endpoints: MASH resolution without worsening of fibrosis and fibrosis improvement (≥1 stage) without worsening of MASH.

Methodology: Following PRISMA guidelines, a systematic search was conducted in PubMed, Embase, PMC, PakMediNet, and Google Scholar from January 2015 to July 2025. Eligible studies included phase 3 randomized controlled trials (RCTs) and network meta-analyses reporting histological outcomes in biopsy-proven MASH. Data on responder rates, relative risks (RR), odds ratios (OR), and surface under the cumulative ranking curve (SUCRA) rankings were extracted from high-quality sources. Random-effects model summaries and heterogeneity assessments (I^2) were noted from published network meta-analyses. Pakistan-specific epidemiological and access data were integrated for contextual relevance.

Results: Network meta-analyses (29 RCTs, n>9,000) ranked pegozafermin highest for both endpoints, followed by tirzepatide, resmetirom, and semaglutide. In MAESTRO-NASH (n=966, F2–F3), resmetirom 100 mg achieved MASH resolution in 29.9% vs. 9.7% placebo and fibrosis improvement in 25.9% vs. 14.2% placebo. In ESSENCE (interim, n=800 at week 72), semaglutide 2.4 mg achieved MASH resolution in 62.9% vs. 34.3% placebo and fibrosis improvement in 36.8% vs. 22.4% placebo. Pioglitazone showed modest effects (RR 2.29 for resolution). In Pakistan, MASLD prevalence ranges 14–38.9%, with limited access to newer agents.

Conclusions: Resmetirom and GLP-1 RAs demonstrate superior histological efficacy compared to pioglitazone. In resource-limited settings like Pakistan, a tiered approach prioritizing affordable therapies, non-invasive monitoring, and local research is recommended to address the growing burden.

Keywords: Metabolic Dysfunction-Associated Steatohepatitis; Resmetirom; Glucagon-Like Peptide-1 Receptor Agonists; Semaglutide; Pioglitazone; Fibrosis.

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INTRODUCTION:

MASLD and its progressive variant MASH are now among the primary contributors to chronic liver conditions worldwide, including in South Asia. Factors such as rapid urban growth, shifts in eating habits, reduced physical activity, and genetic tendencies toward central obesity—even at relatively lower BMIs—have fueled this rise in Pakistan and nearby regions.[1,2]

Estimates suggest MASLD prevalence in Pakistan varies from about 14.8% in adults overall to higher figures (around 19.9%) in those over 40, with South Asian data sometimes reaching 34.7%.[3,4] A substantial subset develops significant fibrosis, leading to more cases of cirrhosis and liver cancer seen in hospitals. Delayed detection is frequent because of inadequate routine screening and a focus on treating advanced symptoms.

Effective medications are now accessible for people with biopsy-verified MASH and F2–F3 fibrosis. This review synthesizes evidence from major RCTs and network meta-analyses on resmetirom, GLP-1 agonists like semaglutide, and pioglitazone, while highlighting practical considerations for Pakistan's healthcare system. [5,6]

METHODOLOGY:

We performed this systematic review in line with PRISMA standards. Literature searches covered PubMed, Embase, PMC, PakMediNet, and Google Scholar between January 2015 and July 2025. Search terms included "resmetirom," "semaglutide," "tirzepatide," "pioglitazone," "MASH resolution," "fibrosis regression," "network meta-analysis," and "Pakistan," combined with appropriate Boolean logic.

Inclusion criteria focused on phase 3 RCTs or network meta-analyses that provided histological data (MASH resolution without fibrosis worsening or ≥1-stage fibrosis improvement without MASH worsening) from adults with biopsy-proven MASH. We also included local epidemiological reports for context. We excluded non-biopsy studies, case reports, and incomplete abstracts.

We pulled key metrics such as response percentages, effect sizes, SUCRA values, and heterogeneity measures (I^2) from established network analyses. Study quality was evaluated with Cochrane Risk of Bias and CINeMA frameworks. Ethical review was not needed.

RESULTS:

Network meta-analyses of 29 RCTs (n>9,000) demonstrated clear rankings. Pegozafermin ranked highest for fibrosis improvement (SUCRA 79.92) and MASH resolution (SUCRA 91.75), followed by tirzepatide, resmetirom, and semaglutide (5). In MAESTRO-NASH (n=966, F2–F3 fibrosis), resmetirom 100 mg achieved MASH resolution in 29.9% (vs 9.7% placebo) and fibrosis improvement in 25.9% (vs 14.2% placebo) (6,7). In ESSENCE interim analysis (n=800 at week 72), semaglutide 2.4 mg achieved MASH resolution in 62.9% (vs 34.3% placebo) and fibrosis improvement in 36.8% (vs 22.4% placebo) (8,9). Pioglitazone showed modest effects (RR 2.29 for MASH resolution). [5,10]

In Pakistan, MASLD prevalence is 14.8% overall, with regional variations and limited access to newer agents. [3,4]

Table 1: Efficacy from Pivotal Trials

Therapy	MASH Resolution (% vs Placebo)[a]	Fibrosis Improvement (% vs Placebo)[b]	Reference
Resmetirom 100 mg	29.9 vs 9.7	25.9 vs 14.2	(6,7)
Semaglutide 2.4 mg	62.9 vs 34.3	36.8 vs 22.4	(8,9)
Pioglitazone	RR 2.29	Modest (OR ~1.8)[c]	(5,10)

[a] Primary endpoint: Resolution of MASH without worsening of fibrosis.

[b] Improvement defined as ≥1 stage improvement in fibrosis without worsening of MASH.

[c] Modest improvement based on odds ratio (OR) from included trials.

RR, relative risk; OR, odds ratio; MASH, metabolic dysfunction-associated steatohepatitis.

Table 2: SUCRA Rankings (Network Meta-Analysis)

Agent	Fibrosis Improvement SUCRA (rank probability)	MASH Resolution SUCRA (rank probability)	Reference
Pegozafermin	79.92 (High)	91.75 (High)	(5)
Tirzepatide	High	84.70 (High)	(5)
Resmetirom	High	High	(5)
Semaglutide	Moderate–High	Moderate	(5)
Pioglitazone	Lower	Modest	(5)

SUCRA, surface under the cumulative ranking curve; MASH, metabolic dysfunction-associated steatohepatitis.
Rank probability: High (≥80%), Moderate–High (50–80%), Moderate (20–50%), Lower (<20%).

DISCUSSION:

Evidence from network meta-analyses indicates that resmetirom and incretin-based therapies (GLP-1 agonists and dual agonists like tirzepatide) generally outperform pioglitazone in promoting MASH resolution and fibrosis regression. [5] Resmetirom targets liver lipid processing directly, whereas GLP-1 agents primarily work via substantial weight reduction and better metabolic control. [6,8]

Given Pakistan's high diabetes burden and MASLD rates around 14.8%, initial management should emphasize lifestyle measures and cost-effective drugs like pioglitazone for suitable patients, with newer agents reserved for those with confirmed advanced disease.[3,4] Models of public-private collaboration used successfully for hepatitis C could help expand availability of advanced options. [11]

Widely available tools such as FIB-4 scores and ultrasound can support patient selection and follow-up in busy clinical settings (12). Safety considerations differ: resmetirom needs thyroid function checks, GLP-1 agents commonly cause digestive side effects (but aid weight loss), and pioglitazone can lead to fluid retention. [6,8]

Differences between rural and urban areas call for broader access to care and innovative screening methods. Local real-world

studies using ward data are urgently needed to assess long-term outcomes in South Asian populations. [13]

There is a pressing need for real-world evidence from Pakistani hospitals to understand outcomes in South Asian groups. National treatment recommendations would help ease pressure on specialist liver services.[5]

Limitations:

This overview draws mainly from existing network meta-analyses. Considerable heterogeneity across studies and the scarcity of Pakistan-specific trials limit generalizability. Most trials are relatively short, so long-term clinical outcomes (such as cirrhosis prevention) remain uncertain.

CONCLUSIONS:

Resmetirom and GLP-1 receptor agonists offer stronger histological benefits than pioglitazone. Implementing practical, locally tailored strategies combined with targeted research will be vital for managing the rising MASH burden in Pakistan.

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Conflicts of Interest: None declared.

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Author's Contribution:

SUQ: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

KAK, RK, AW, HA: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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