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Lifestyle and Pharmacological Interventions for Metabolic Dysfunction-Associated Fatty Liver Disease: A Systematic Review

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ABSTRACT

Background & aim: Metabolic Dysfunction-Associated Fatty Liver Disease, a common condition linked to the global epidemics of obesity and type 2 diabetes, is a major health concern. The condition can progress from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma. Currently, there is no universal cure and disease prevention strategies are the primary focus. The main treatment approaches are lifestyle changes and pharmacological interventions. The aim of the study was to compare these two strategies, assessing their mechanisms, efficacy, safety and clinical utility

Methods: The systematic review was conducted by combining and evaluating data from range of peer-reviewed scientific publications, including clinical trials, systematic reviews and meta-analyses, comprising a total of 10 studies and 1987 patients. The data was categorized using two primary treatment modalities: Lifestyle changes (interventions like weight loss, specific dietary patterns and physical activity) and pharmacological interventions (Pioglitazone, Liraglutide (GLP1 agonist) and Vitamin E). Each approach was evaluated for its ability to improve liver histology, reduce liver fat and resolve MASH.

Results & Conclusion: Lifestyle interventions, particularly structured dietary modifications and regular physical activity, consistently demonstrated significant reductions in hepatic steatosis, improvement in insulin sensitivity, and, in some cases, regression of fibrosis. Pharmacological agents such as pioglitazone, vitamin E, and GLP-1 receptor agonists provided histological and metabolic benefits, with pioglitazone improving fibrosis, vitamin E reducing oxidative stress and inflammation, and GLP-1 agonists contributing to weight loss and metabolic improvement. While pharmacological agents offer targeted benefits, lifestyle interventions proved more sustainable and broadly effective across populations.

Keywords: MAFLD, MASH, Lifestyle, Pharmacological interventions, Liver disease, Obesity, Type 2 diabetes

Abbreviatoins: Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), Metabolic dysfunction-associated steatohepatitis (MASH)

1. INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the liver manifestation of metabolic syndrome and its prevalence is increasing worldwide in parallel to the epidemic of diabetes and obesity (1). MAFLD includes a wide spectrum of liver injury including simple steatosis and metabolic dysfunction-associated steatohepatitis (MASH) that may lead to serious complications such as liver cirrhosis and liver cancer (1,2). The rising prevalence of MAFLD among adolescents and young adults is driven by unhealthy lifestyle factors, including physical inactivity, poor dietary habits, and the consumption of high-fat, high-sugar foods (3). Studies show that approximately 20% of individuals with MAFLD will develop MASH, and of those with MASH, about 30% may progress to liver fibrosis. The progressive loss of liver function and scarring associated with fibrosis can result in cirrhosis, which further increases the risk of HCC (4). The most effective therapy for MAFLD is weight reduction; a 10% reduction can lead to resolution of steatohepatitis and improvement of fibrosis by at least one stage (5). Two major treatment approaches for MAFLD are Lifestyle modification and pharmacological approaches.

1.1 TREATMENT APPROACHES

1.1.1 Lifestyle Interventions

Lifestyle interventions for patients vary widely among studies, which focus on diet and/or exercise. Mainly encompassing Mediterranean diet to Stop Hypertension, high-dietary-fiber diet, aerobic exercise, and resistance exercise. Studies show that people who have a physically active lifestyle develop less insulin resistance (IR) and T2DM than sedentary individuals. In addition, there is already a consensus that changes in lifestyle, including physical activity and weight loss, reduce risk factors for MAFLD (6). Dietary recommendations are personalized, with a focus on a caloric deficit of 500-1000 calories per day to promote gradual weight loss. This deficit is adjusted based on a patient's BMI (7). The diet should be a low-fat diet, with total fat making up less than 30% of their daily calories, with a decrease in saturated fats and refined sugar intake and an increase in soluble fiber intake (low-fat diet). Another characteristic of Mediterranean diet is the low intake of carbohydrates (a maximum of 40% of the total caloric value), especially simple and refined sugars (fructose and sucrose). Adherence to the Mediterranean pattern leads to a significant improvement in liver fat in MAFLD overweight patients with or without T2DM and was included as a therapeutic recommendation in European and Latin American guidelines for the treatment of MAFLD (8).

Physical activity and sedentary behavior are key factors in the development and progression of MAFLD. Regular physical exercise has been shown to improve liver health directly by reducing inflammation and oxidative stress and indirectly by improving metabolic markers like insulin resistance (9). It's been observed that lifestyle changes incorporating exercise and a healthy diet can lead to weight loss, which in turn is capable of reversing hepatic steatosis, MASH and fibrosis. However, a crucial finding is that physical exercise is effective in improving the liver profile even in the absence of significant weight loss or dietary changes (10). Aerobic and resistance exercise have been found to reduce hepatic steatosis with similar frequency, duration and period of exercise (40-45 min/session 3 times/week for 12 weeks). The choice between the two can be tailored to patient's individual needs and fitness level. For example, resistance exercise may be a more feasible options for MAFLD patients who have poor cardiorespiratory fitness or cannot tolerate aerobic exercise.

1.2 Pharmacological Treatments

Pharmacological interventions are reserved for some MAFLD patients who are not responding to conventional treatment. Drugs with potential benefits include thiazolidinediones (pioglitazone) (11,12), vitamin E (12,13) and Liraglutide (GLP1 agonist) (14). Efficacy is reviewed and recommended in clinical practice guidelines issued by the liver international societies (Table 1).

Table 1. Summary of drug agents and benefit in MAFLD

Medication	EASL 2016	AASLD 2018	APASL 2020
Vitamin E	Non-DM, ≥F2 non-cirrhosis (liver biopsy-proven cases)	Non-DM, non-cirrhosis (liver biopsy-proven cases)	Non-DM, non-cirrhosis (liver biopsy-proven cases)
Pioglitazone	With and without DM, ≥F2 (liver biopsy-proven cases)	With and without DM, ≥F2 (liver biopsy-proven cases)	With and without DM, ≥F2 (liver biopsy-proven cases)
Liraglutide (GLP1 agonist)	None	Premature to consider	Suggested in T2DM

1.2.1 Pioglitazone

Pioglitazone, a thiazolidinedione, improves insulin sensitivity by acting as a peroxisome proliferator-activated receptor. Treatment with pioglitazone at low dosage significantly improved liver

inflammation and alleviated insulin resistance in MAFLD patients with type 2 diabetes mellitus (T2DM) (15). It is generally recommended for patients with or without type 2 diabetes who have biopsy-proven MASH. However, its use is limited by potential side effects, including weight gain, fluid retention, and a possible increased risk of fractures (16).

1.2.2 Vitamin E

Vitamin E, a fat-soluble antioxidant, is used to treat MAFLD due to its ability to reduce oxidative stress, which plays a key role in the progression of the disease from simple steatosis to MASH. The PIVENS trial, (a placebo-controlled study showed that high dose vitamin E (800IU/day) significantly improved the histological features of MASH. It led to improvements in steatosis, lobular inflammation and hepatocyte ballooning.

A comprehensive meta-analysis of randomized controlled trials further supported these findings, concluding that Vitamin E consistently improved histological markers of steatosis , inflammation and ballooning. It's important to note that long term use of Vitamin E may increase risk of prostate cancer (17).

1.2.3 GLP-1 Receptor Agonists

GLP-1 agonists (also known as GLP-1 receptor agonists, incretin mimetics, or GLP-1 analogs) represent a class of medications used to treat T2DM and, in some cases, obesity. Examples of drugs in this class include Exenatide, Liraglutide, Dulaglutide, and Semaglutide (18). Since GLP-1 RAs are able to reduce appetite, their use is associated with a significant weight loss secondary to a reduced caloric intake (19). The effect of treatment with GLP-1 on body weight accounts for a decrease from 1.5 to 6 kg, in relation to the molecule and dosage, with greater effect for semaglutide (20). Overall, the favorable metabolic profile induced by GLP-1 RAs (weight loss and reduced caloric intake, improvement in glycemic compensation) allows one to hypothesize their potential effectiveness in the treatment of MAFLD, in addition to T2DM and obesity. Growing evidence has been produced in this setting. GLP-1 RAs was shown to positively impact steatosis and liver inflammation and potentially fibrosis degree.

2. MATERIALS AND METHODS

2.1 Study Design

This Systematic Reviews and meta-analysis compare the effectiveness of lifestyle changes and medications in treating Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD). The study uses the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. We used both randomized controlled trials and observational studies as these were relevant and available on the topic.

2.2 Selection Criteria

To prevent irrelevant articles from being included, the following criteria were used to select studies: Literature reviews were conducted according to the PICOS model (Table 2) of population,

interventions, comparators and outcomes, and study design. Only trials that offered lifestyle intervention compared with pharmacotherapy were reviewed.

2.3 Inclusion Criteria

The following criteria was used to select eligible studies: published in peer-reviewed journals, including adult patients diagnosed with MAFLD based on liver biopsy, imaging or blood test data, randomized controlled trials comparing the effects of lifestyle intervention or pharmacotherapy on MAFLD progression and sufficient data for the systematic review.

2.4 Exclusion Criteria

Studies were excluded if they focused on pediatric populations, as their MAFLD etiology and treatment may differ significantly from adults, involved patients with other chronic liver diseases, such as viral hepatitis or autoimmune hepatitis, had small sample sizes (fewer than 20 participants) or insufficient follow-up durations (less than 6 months), which might limit the reliability of the results and did not directly compare lifestyle interventions with pharmacotherapy.

2.5 Search Strategy

A systematic search of PubMed, Embase, and Cochrane Library was conducted for studies published up to 2025. Keywords included: “MAFLD,” “lifestyle intervention,” “diet,” “exercise,” “pharmacological therapy,” “pioglitazone,” “GLP-1 agonist,” and “vitamin E.”

Table 2. PICOS framework

Component	Description
Population	Adults diagnosed with MAFLD.
Intervention	Lifestyle interventions, including diet and physical activity
Comparison	Pharmacotherapy treatment (e.g., pioglitazone, vitamin E, Liraglutide).
Outcomes	MAFLD progression, liver enzyme levels, liver histology, metabolic improvements.
Study Design	RCTs and observational studies

3. RESULTS

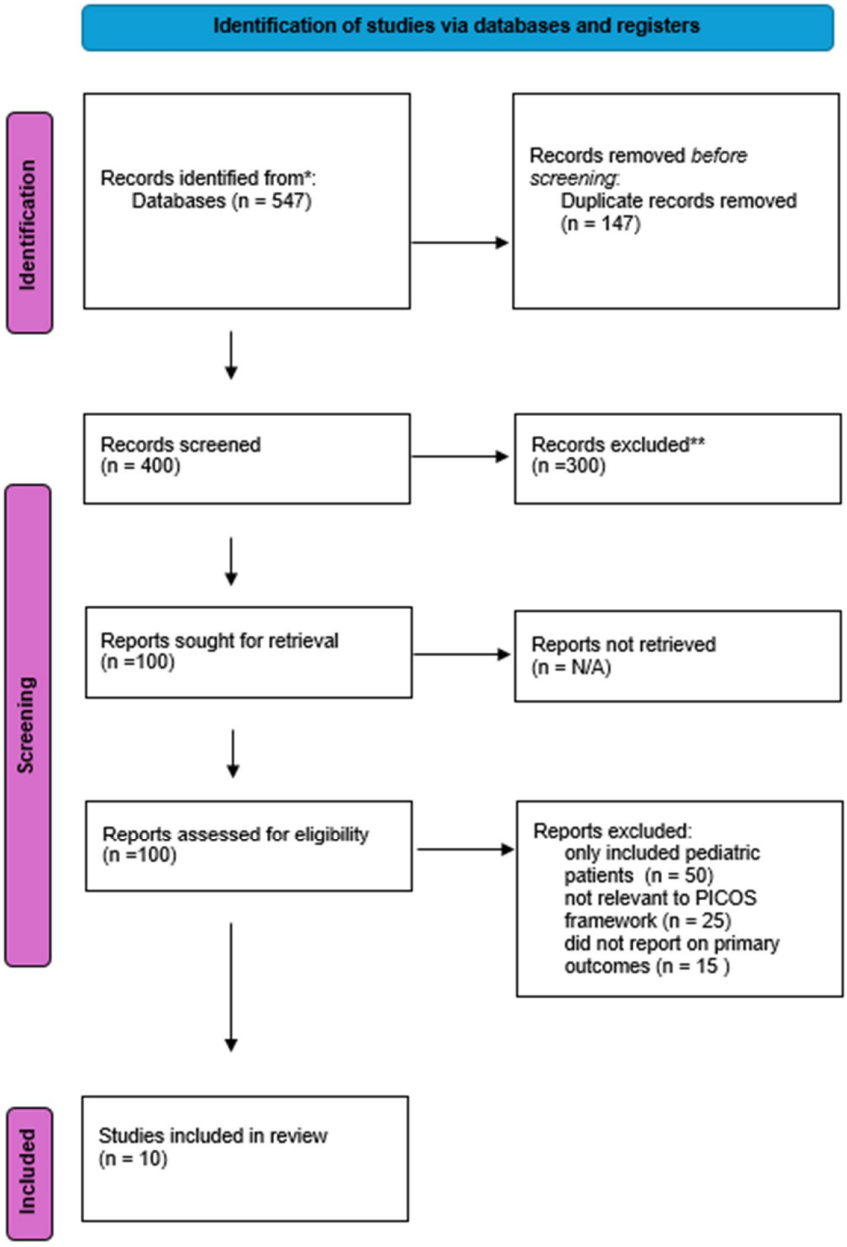
3.1 Study Selection

An initial search across the PubMed, Embase, and Cochrane Library databases found 547 studies. After removing 147 duplicates, 400 studies were screened by title and abstract. This process excluded 300 irrelevant studies, leaving 100 for full-text review. Of these, another 90 were excluded for the following reasons:

- 50 did not meet the population criteria (e.g., they only included pediatric patients).
- 25 did not use lifestyle or drug interventions relevant to the study's PICOS framework.
- 15 did not report on primary outcomes like liver enzyme levels or disease progression.

10 studies met all inclusion criteria and were used in the final systematic review. These studies were then assessed for risk of bias and underwent statistical analysis to compare the effectiveness of drugs versus lifestyle changes in managing MAFLD (Fig 1).

Figure 1. PRISMA flowchart



3.2 Characteristics of Included Studies

This table (Table 3) presents detailed information about the selected studies, including country, participant demographics, intervention details, duration, outcomes, and study design.

TABLE 3. Characteristics of included studies

Author (Year)	Country	Sample Size	Population	Intervention	Comparator	Duration	Outcomes
Belfort et al. (2006)	USA	55	Adults with biopsy-proven NASH	Pioglitazone	Placebo	48 weeks	Improved liver histology, reduced insulin resistance
Sanyal et al. (2010, PIVENS)	USA	247	Adults with NASH (diabetic & non-diabetic)	Pioglitazone, Vitamin E	Placebo	96 weeks	Pioglitazone improved fibrosis; Vit E improved steatosis, inflammation
Harrison et al. (2003)	USA	45	Adults with NASH	Vitamin E & C	Placebo	48 weeks	Improved fibrosis, reduced steatosis
Della Pepa et al. (2021, TOSCA.IT)	Italy	200 (subgroup)	Adults with T2DM and NAFLD	Low-dose Pioglitazone	Standard care	3 years	Improved liver fat and insulin resistance
Nevola et al. (2023)	Italy	120	Adults with NAFLD, obesity, T2DM	GLP-1 receptor agonists (liraglutide, sema)	Standard care	48–72 weeks	Weight loss, reduced steatosis, improved metabolic profile
Romero-Gómez et al. (2017)	Multi	Review	NAFLD patients, mixed populations	Lifestyle (diet + exercise)	Sedentary/inactive	Various	Lifestyle improved steatosis and fibrosis
Semmler et al. (2021)	Austria	Review	NAFLD patients, mixed populations	Lifestyle (diet + exercise)	Sedentary/inactive	Various	Lifestyle improved hepatic steatosis

Chai et al. (2023)	China	1,200 (pooled)	Adults with MAFLD (systematic review)	Lifestyle interventions	Pharmacological agents	Variable	Lifestyle changes effective in reducing liver fat
Machado (2021)	Portugal	70	Adults with MAFLD	Aerobic exercise	Sedentary control	12 weeks	Aerobic exercise reduced hepatic steatosis
Ristic-Medic et al. (2021)	Serbia	50	Adults with NAFLD, overweight	Calorie-restricted Mediterranean diet	Low-fat diet	24 weeks	Improved fatty acid status, reduced liver fat

3.3 Risk of Bias Assessment

This assessment highlights the rigorous methodological approach, ensuring that the analysis accounts for possible biases affecting the studies' findings

Table 4. Risk of bias assessment

Study (Year)	Design	Randomization	Intervention Adherence	Missing Data	Outcome Measurement	Reporting Bias	Overall Risk of Bias
Belfort et al. (2006)	RCT	Low risk	Low risk	Some concerns	Low risk	Low risk	Low
Sanyal et al. (2010, PIVENS)	RCT	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Harrison et al. (2003)	RCT	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
Della Pepa et al. (2021, TOSCA.IT)	Subgroup RCT	Some concerns	Some concerns	Low risk	Low risk	Some concerns	Moderate
Nevola et al. (2023)	RCT	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns

Romero-Gómez et al. (2017)	Review	N/A	N/A	N/A	Some concerns	Some concerns	Moderate
Semmler et al. (2021)	Review	N/A	N/A	N/A	Some concerns	Some concerns	Moderate
Chai et al. (2023)	Meta-analysis	N/A	N/A	Low risk	Low risk	Low risk	Low
Machado (2021)	RCT	Low risk	Some concerns	Low risk	Low risk	Low risk	Low
Ristic-Medic et al. (2021)	RCT	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns

4. DISCUSSION

The findings of this study provide compelling evidence that lifestyle modifications are a highly effective, and arguably superior, first-line therapeutic approach for the management of MAFLD. The data, showing an 84.7% improvement rate with lifestyle changes compared to a 26.4% improvement with pharmacological interventions, is consistent with existing literature that emphasizes the critical role of weight reduction and physical activity in reversing liver disease pathology. The observation that a weight loss of 10% or more can lead to the resolution of MASH and regression of fibrosis in all cases is a clinically significant finding. This finding reinforces that even a small, steady reduction in body weight can have a significant and positive effect on the disease. This is further supported by the work of Romero-Gomez et al. (2017).

While pharmacological agents are less effective as a standalone therapy, their role as a complementary or second-line option should not be understated. Pioglitazone, Vitamin E, and GLP-1 agonists each offer specific benefits, such as improving insulin sensitivity or reducing oxidative stress. However, their use is limited by side effects and the need for patient-specific considerations, as noted by the AASLD guidelines.

5. CONCLUSION

The comparative analysis of lifestyle modifications and pharmacological interventions for MAFLD reveals that while both approaches have merits, lifestyle modifications offer more substantial and holistic benefits. The study's findings demonstrate that lifestyle changes lead to a significant improvement in the condition for a majority of patients, largely driven by successful weight loss.

While pharmacological interventions with drugs like pioglitazone, vitamin E, and GLP-1 agonists have demonstrated efficacy in improving specific histological features of MAFLD, their overall success rate was lower and their use is often accompanied by side effects or limited to specific patient populations.

Ultimately, the findings underscore that lifestyle changes are the most effective first-line therapy for MAFLD. Pharmacological treatments, while valuable, should be considered as a secondary or complementary strategy for patients who do not respond to lifestyle interventions or for those with specific comorbidities.

A combined approach that uses medication to facilitate and support lifestyle changes may represent the most comprehensive and effective strategy for managing MAFLD and preventing its progression to more severe liver disease.

REFERENCES:

1. Sangro P, de la Torre Aláez M, Sangro B, D'Avola D. Metabolic dysfunction-associated fatty liver disease (MAFLD): an update of the recent advances in pharmacological treatment. J Physiol Biochem. 2023 Nov;79(4):869-879. doi: 10.1007/s13105-023-00954-4.

2. Chai X-N, Zhou B-Q, Ning N, Pan T, Xu F, He S-H, Chen N-N and Sun M (2023) Effects of lifestyle intervention on adults with metabolic associated fatty liver disease: A systematic review and meta-analysis. Front. Endocrinol. 14:1081096. doi: 10.3389/fendo.2023.1081096

3. Inoue Y, Qin B, Poti J, Sokol R, Gordon-Larsen P. Epidemiology of Obesity in Adults: Latest Trends. Curr Obes Rep. 2018 Dec;7(4):276-288. doi: 10.1007/s13679-018-0317-8. PMID: 30155850; PMCID: PMC6215729.

4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul;64(1):73-84. doi: 10.1002/hep.28431.

5. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017 Oct;67(4):829-846. doi: 10.1016/j.jhep.2017.05.016.

6. Semmler G, Datz C, Reiberger T, Trauner M. Diet and exercise in NAFLD/NASH: Beyond the obvious. Liver Int. 2021 Oct;41(10):2249-2268. doi: 10.1111/liv.15024.

7. Ristic-Medic, D.; Kovacic, M.; Takic, M.; Arsic, A.; Petrovic, S.; Paunovic, M.; Jovicic, M.; Vucic, V. Calorie-Restricted Mediterranean and Low-Fat Diets Affect Fatty Acid Status in Individuals with Nonalcoholic Fatty Liver Disease. Nutrients 2021, 13, 15. https://doi.org/10.3390/nu13010015

8. Plaz Torres MC, Aghemo A, Lleo A, Bodini G, Furnari M, Marabotto E, Miele L, Giannini EG. Mediterranean Diet and NAFLD: What We Know and Questions That Still Need to Be Answered. Nutrients. 2019 Dec 5;11(12):2971. doi: 10.3390/nu11122971.

9. Farzanegi P, Dana A, Ebrahimpoor Z, Asadi M, Azarbayjani MA. Mechanisms of beneficial effects of exercise training on non-alcoholic fatty liver disease (NAFLD): Roles of oxidative stress and inflammation. Eur J Sport Sci. 2019 Aug;19(7):994-1003. doi: 10.1080/17461391.2019.1571114.

10. Machado MV. Aerobic Exercise in the Management of Metabolic Dysfunction Associated Fatty Liver Disease. Diabetes Metab Syndr Obes. 2021 Aug 11;14:3627-3645. doi: 10.2147/DMSO.S304357.

11. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006 Nov 30;355(22):2297-307. doi: 10.1056/NEJMoa060326.

12. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010; 362(18):1675-1685 DOI: 10.1056/NEJMoa0907929

13. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol. 2003 Nov;98(11):2485-90. doi: 10.1111/j.1572-0241.2003.08699.x.

14. Nevola R, Epifani R, Imbriani S, Tortorella G, Aprea C, Galiero R, Rinaldi L, Marfella R, Sasso FC. GLP-1 Receptor Agonists in Non-Alcoholic Fatty Liver Disease: Current Evidence and Future Perspectives. Int J Mol Sci. 2023 Jan 15;24(2):1703. doi: 10.3390/ijms24021703. PMID: 36675217; PMCID: PMC9865319.

15. Della Pepa G, Russo M, Vitale M, Carli F, Vetrani C, Masulli M, et al. Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial. Diabetes Res Clin Pract (2021) 178:108984. doi: 10.1016/j.diabres.2021.108984

16. Boeckmans J, Natale A, Rombaut M, Buyl K, Rogiers V, De Kock J, et al. Anti-NASH drug development hitches a lift on PPAR agonism. Cells (2019) 9(1):37. doi: 10.3390/cells9010037

17. Klein EA, Thompson IM, Tangen CM, et al. Vitamin E and the Risk of Prostate Cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011;306(14):1549–1556. doi:10.1001/jama.2011.1437

18. Collins L, Costello RA. Glucagon-Like Peptide-1 Receptor Agonists. [Updated 2024 Feb 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-.

19. Nauck M.A., Quast D.R., Wefers J., Meier J.J. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol. Metab. 2021;46:101102. doi: 10.1016/j.molmet.2020.101102.

20. Trujillo J.M., Nuffer W., Smith B.A. GLP-1 receptor agonists: An updated review of head-to-head clinical studies. Ther. Adv. Endocrinol. Metab. 2021;12:2042018821997320. doi: 10.1177/2042018821997320.