Therapeutic Quiver of Non-Alcoholic Fatty Liver Disease

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The therapeutic quiver of nonalcoholic fatty liver disease (NAFLD) consists of several levels, of which lifestyle, pharmaceutical, and surgical approaches are the main treatments. A multimodal intervention with multiple aspects, such as lifestyle modification, weight loss, specific diets, and medication, is the most appropriate and holistic approach for most people with NAFLD.

Keywords: fatty liver disease ; fibrosis ; resolution of NAFLD ; diabetes mellitus

1. Less Is More: Unlocking the Power of Conservative Treatment

1.1. The Power of Lifestyle Modification in NAFLD

Robust evidence supports the crucial role of lifestyle changes as primary options for the treatment of nonalcoholic fatty liver disease (NAFLD). These approaches, which include diet, exercise, or physical activity, mainly aim to control metabolic status [1]. Looking back in 2004, the World Health Organization (WHO) established that moderate intensity exercise improves not only physical and mental health, but also metabolic syndrome, T2DM, and cardiovascular disease, conditions that are inseparably related to NAFLD [2]. In the 21st century, physical activity is considered a pillar determinant of metabolic control and is recommended for NAFLD. Different types of exercise, such as high-intensity intermittent exercise, aerobic exercise, or resistance exercise, seem to have beneficial effects on fatty liver disease [3][4]. In 2017, Oh et al. found that high-intensity interval aerobic exercise, moderate-intensity continuous aerobic exercise, and resistance exercise were equally effective in decreasing liver fat content. However, only high-intensity interval aerobic exercise had a beneficial effect on restoring Kupffer cell function [5]. A randomized control trial by Zhang et al. indicated that after a 12-month active intervention, the two exercise groups (strong and moderate training) showed a significant reduction in intrahepatic triglyceride content (measured by proton magnetic resonance spectroscopy) compared to the control group [6]. Furthermore, several studies reported that resistance training leads to a reduction in liver fat of 4–47% independently of weight loss [7]. The mechanisms underpinning the reduction of hepatic fat deposition due to exercise reflect changes in insulin sensitivity and circulatory lipids. Exercise not only improves glycemic control but suppresses de novo lipogenesis and improves blood pressure levels in people with NAFLD [8][9][10].

1.2. Shedding Pounds: The Science of Weight Loss and Calorie Restriction

Weight loss is a gold standard therapy for most patients with NAFLD and can regress liver disease, along with the reduction of cardiovascular disease and the risk of T2DM [11]. Some researchers support that a weight reduction of 10% is capable of inducing the resolution of NASH and improving fibrosis by at least one stage [12]. According to the guidelines of the American Association for the Study of Liver Diseases (AASLD), a weight loss of 5–10% in overweight or obese individuals and 3–10% in non-obese individuals with NAFLD is the primary objective of lifestyle interventions. In accordance with the above, there are also the National Institute of Health and Care Excellence (NICE) guidelines [13][14]. In addition, obesity, as a result of excess caloric consumption, is one of the leading factors for NAFLD. Caloric restriction acts on metabolic reprogramming and on the utilization of body energy, reducing oxidative damage to cells [15]. Because carbohydrates (which are the main energy source of the human body) are linked to NAFLD, their restriction in the diet can lead to lower glycemic load, increased insulin sensitivity, and pancreatic β-cell insulin secretion of pancreatic cells [16].

A clinical trial by Holmer et al., which recruited 74 patients with NAFLD, indicated that intermittent calorie restriction and a low carbohydrate high fat diet (LCHF) are more effective in reducing liver steatosis and body weight compared to general lifestyle modification. Participants were randomized into 3 groups: intermittent calorie restriction, including 500 kcal/day for women and 600 kcal/day for men; LCHF, with an average daily calorie intake of 1600 kcal/day for women and 1900 kcal/day for men; and general lifestyle advice [17]. Furthermore, in a prospective study by Vilar et al., a combination of

exercise and a hypocaloric diet revealed a dose–response relationship between weight reduction and general histological parameters, with the greatest improvement detected in those with the greatest weight loss [18]. However, the beneficial effects of a low-carbohydrate diet are only in the short term. In the long term, a reduced carbohydrate and a reduced fat diet has results similar to those who achieved a 7% weight loss [19].

In addition to the above, it should be noted that some studies reported the beneficial effect of diabetes remission on NAFLD and pancreatic morphology. In 2020, a post hoc analysis of the DiRECT trial showed changes in the gross morphology of the pancreas 2 years post T2DM remission. The size of the pancreas had increased in patients who achieved remission and weight loss, compared to those who did not respond to the weight loss intervention. Intrahepatic fat and levels of FGF-21 and FGF-19 also decreased. However, it is notable that there is no significant increase in pancreas volume after 6 months of reversal of type 2 diabetes [20]. Additional trials might be of interest from a scientific point of view to investigate further data on the progression of NAFLD and changes in pancreatic tissue after remission of diabetes.

1.3. Breaking the Link between Fatty Liver and Type 2 Diabetes: The Power of Nutritional Interventions

Numerous studies have corroborated the pivotal role of certain macronutrients in the initiation and progression of NAFLD, regardless of caloric intake. In particular, macronutrients such as saturated fatty acids (SFA), trans fats, simple sugars such as sucrose and fructose, and animal proteins are known to inflict damage on the liver through the accumulation of triglycerides and impaired antioxidant activity, compromising insulin sensitivity and postprandial triglyceride metabolism [21]. In contrast, the consumption of monounsaturated fatty acids (MUFA), ω3 polyunsaturated fatty acids (PUFA), plant-based proteins, and dietary fibers such as whole grain cereals, fruits and vegetables, fatty fish (which are primarily rich in ω3), and extra virgin olive oil have been found to confer beneficial effects [22][23]. Gupta et al. suggest that oily fish (2–4 g/d), coffee (≥3 cups/day), and nuts (100 g/d) are recommended as suitable additions to physical activity and caloric restriction for patients with fatty liver disease, based on strong evidence from human trials. Although tea, red wine, avocado and olive oil can be consumed moderately without harm, more research is needed to investigate their therapeutic benefits for patients with NAFLD/NASH [24].

Furthermore, Halima et al. conducted a study investigating the impact of apple cider vinegar on rats with diabetes and demonstrated that in addition to its potent antihyperglycemic properties, it also exhibited a crucial hepatoprotective effect. In particular, indicators of liver toxicity, namely ALT, AST, total and direct bilirubin, as well as levels of TC, TG, and LDL-c, demonstrated a significant reduction, which was particularly prominent after four weeks of treatment, together with an elevation in HDL-c [25]. These findings are consistent with several other studies [26][27][28]. The above elucidated results unequivocally demonstrate that daily ingestion of vinegar can mitigate the increase in blood glucose levels and lipid profile, which is typically induced by a hypercaloric diet in rats, as posited by Ousaaid et al. [29]. Therefore, the use of apple cider vinegar could confer considerable advantages in avoiding metabolic irregularities commonly associated with a high-calorie diet.

2. Cutting-Edge Solutions: Exploring Surgical Therapies for NAFLD

The potential effects of bariatric surgery on liver fat disease may extend beyond weight loss. In fact, serum concentrations of glucagon-like peptide-1 (GLP-1) increase after metabolic surgery, leading to decreased appetite, slower gastric emptying, and improved insulin sensitivity [30]. Furthermore, the main role of GLP-1 is to modulate bile acid signaling through the farnesoid X receptor (FXR), which can modify the gut microbiome and promote NAFLD [31]. Therefore, current guidelines recommend that metabolic surgery can be a potential approach in patients with T2DM or overweight/obese individuals (i.e., BMI > 35 kg/m^2) [13][32]. Although bariatric surgery has a beneficial effect, various limitations such as patient acceptability of complications, availability of services, and high cost make its use difficult and highlight the need to carefully select eligible candidates [33].

The most common bariatric surgery procedures include adjustable gastric band (AGB), biliopancreatic diversion (BPD), vertical sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). Consequently, different methods might induce variable biological effects depending on the surgical procedure. The most common metabolic operations are SG and RYGB. In the first, about 80% of the stomach portion is removed along the gastric greater curvature and the small dimensions of the stomach, along with the changes in the hormonal environment, reduce hunger and delay gastric emptiness. In the second procedure, the stomach is separated into a smaller pouch in the smaller curvature (through stapling) and anastomosed with the jejunum [34][35]. In fact, by restricting food intake and by promoting malabsorption of nutrients, these techniques can cause weight loss. Both the reduction in body weight and decrease in waist circumstance

through bariatric surgery led to improvement in insulin resistance, T2DM, obesity, fatty liver disease, and dyslipidemia [33]. Interestingly, one of the most important outcomes of bariatric surgery is that it can markedly improve all histological characteristics of NAFLD, including fibrosis. According to Lee et al., a resolution of steatosis was observed in 66% of patients, a resolution of inflammation in 50% of patients, and a resolution of fibrosis in 40% of patients after bariatric surgery [36]. Another recent study published in 2018, showed a resolution of NAFLD of 78% after RYGB [37]. Furthermore, Weiner reported that patients after AGB, RYGB and BPD achieved complete regression of NAFLD in up to 82.8% of the cases [38].

3. Exploring the Innovative World of Pharmaceutical Solutions

3.1. Effects of Anti-Diabetic Agents on NAFLD

It is well established that fatty liver and T2DM are the two sides of the same coin, sharing common pathogenic pathways and factors such as insulin resistance. Although the coexistence of fatty liver and T2DM is increasing, the treatment is not adequate. Due to this close link between T2DM and NAFLD, various glucose-lowering drugs have been used as NAFLD therapeutics. Numerous clinical trials have shown the beneficial effects of GLP-1 receptor agonists, insulin-sensitizing thiazolidinediones, and sodium-glucose cotransporter 2 (SGLT2) inhibitors on liver fat content. GLP-1 binds to a specific GLP-1 receptor, whose activation can promote the reduction of liver steatosis by improving insulin signaling pathways, hepatocyte lipotoxicity, and mitochondrial function [39][40]. On the contrary, SGLT2 inhibition promotes negative energy balance through increased glycosuria and a change of the substrate to lipids as an energy source, which inhibit liver steatosis, inflammation, and fibrosis [41]. In 2021, a meta-analysis by Mantovani et al. showed that treatment with GLP-1 receptor agonists or SGLT2 inhibitors compared to placebo decreased the absolute percentage of liver fat content and serum levels of ALT [42]. These findings have been replicated by several other studies [43].

It is significant to mention that a multitude of studies have recently elucidated the efficacy of SGLT2 inhibitors in alleviating liver steatosis. Of particular interest, in 2018, Shibuya et al. revealed, for the first time, the statistically significant and advantageous impact of luseogliflozin, compared to metformin, on NAFLD and weight loss [44]. The results manifested a superior effect of the former, particularly on body mass index (BMI), after a six-month period. Luseogliflozin facilitates the mitigation of visceral adiposity by excreting energy through urine glucose excretion [44]. Additionally, in the same year, a double-blind randomized controlled study revealed that dapagliflozin monotherapy can reduce the levels of hepatocyte injury biomarkers, such as ALT, AST, γ-glutamyl transferase (γ-GT), cytokeratin 18-M30, cytokeratin 18-M65, and plasma fibroblast growth factor 21 (FGF21). With the combination of omega-3 carboxylic acids, not only can glucose control be improved, but body weight and abdominal fat volumes can also be reduced [45]. Analogous results were observed in a study by Sattar et al. using empagliflozin, in which the decline in ALT was consistently more notable than that of AST. The reductions were most prominent in participants with the highest baseline ALT levels and were primarily unaffected by changes in HbA1c and body weight [46]. However, the exact mechanisms through which empagliflozin mitigates aminotransferases or liver fat remain ambiguous; therefore, more research is needed.

Thiazolidinediones increase peripheral insulin sensitivity by stimulating adipokines, promoting triglyceride storage in adipose tissue, and improving the suppressive action of insulin on lipolysis [47]. In this way, thiazolidinediones lead to lower serum levels of free fatty acids and reduced hepatic lipid accretion [47]. The most common and approved are pioglitazone and rosiglitazone, which are powerful activators of the nuclear receptor PPARγ and are expressed mainly in adipose tissue [48]. Numerous studies have shown that pioglitazone has a beneficial effect on insulin sensitivity, inflammation, and hepatocyte degeneration, but there was no difference in the resolution of fibrosis [49]. A recent meta-analysis of randomized controlled trials using pioglitazone or rosiglitazone revealed that both drugs led to enhanced liver histology, including decreased steatosis, inflammation, and hepatocyte degeneration [50].

Recently, semaglutide and tirzepatide have been added to the therapeutic quiver against T2DM and obesity. Semaglutide is a GLP-1 analogue, and tirzepatide is a dual analogue of GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) [51]. Both delivered impressive results in the phase 3 trials and can be considered future game changers in the realm of T2DM remission. Due to their importance in NASH therapy, these agents will be discussed in detail at a later part of the research.

3.2. Effects of Statins and Other Lipid-Lowering Drugs

Realizing that NALFD is strongly related to metabolic syndrome, there is a need for an integrated approach for individuals with a high liver fat content. The definition of metabolic syndrome includes the following criteria: abdominal obesity, with waist circumference of ≥90 cm in men or ≥85 cm in women; low high-density lipoprotein (HDL) cholesterol with HDL-cholesterol of <40 mg/dL in men and <50 mg/dL in women; hypertriglyceridemia with triglyceride (TG) of ≥150 mg/dL; high

systolic blood pressure (BP), with systolic BP of ≥130 mmHg and/or diastolic BP of ≥85 mmHg; or hyperglycemia, with fasting plasma glucose (FPG) of >100 mg/dL [52][53]. Consequently, abnormal blood cholesterol levels play a key role in the progression of NAFLD and can be controlled with statins [54]. Except for this action, statins exhibit pleiotropic properties, such as antioxidant and anti-inflammatory effects, neoangiogenesis, and improvement of endothelial functions [54]. Interestingly, a large amount of data recommended that a statin remedy is correlated with a significant improvement in liver steatosis, inflammation, and even fibrosis [55][56]. For example, an observational study by Lee et al. found a lower risk of NAFLD in patients who received statin therapy [56]. According to a meta-analysis of six studies, ezetimibe, which is a lipid lowering agent acting by reducing cholesterol absorption in the intestines, significantly reduced plasma liver enzyme levels, as well as improved liver steatosis [57]. On the contrary, fenofibrate, a PPAR-a agonist, does not have a significant effect on liver fat content [58].

Furthermore, the category of omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as a-linolenic acid (a-ALA), stearidonic acid (SDA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), has a beneficial effect on peripheral insulin sensitivity and on triglycerides levels, leading to a lower deposition of liver fat [59]. A randomized control trial published in 2020 reported lower liver fat in patients who received n-3 PUFA supplementation compared to those who received the placebo [59]. Similar outcomes were observed in another meta-analysis [60]. However, more well-designed randomized clinical trials are necessary to suggest omega-3 PUFA supplementation for the treatment of NAFLD in patients with and without T2DM.

Although statins have long been used as a widely accepted method for reducing cholesterol and minimizing the risk and mortality associated with cardiovascular disease, recent years have seen increasing scrutiny of their potential side effects. It should be noted, in particular, the increasing evidence linking prolonged statin use with diabetes progression and ectopic fat deposition, particularly in the kidneys of patients with diabetic nephropathy [61]. Recently, a study by Huang et al. revealed that statin administration for a period of more than 10 years was found to increase insulin resistance, alter lipid metabolism, provoke inflammation and fibrosis, and ultimately exacerbate the progression of diabetic nephropathy in diabetic mice. It is worth noting that the duration of the study spanned 50 weeks, which is equivalent to at least 35 years in the human life cycle [61]. Similar results were reported in the retrospective cohort study by Mansi et al., which followed patients with diabetes for a 12-year period and highlighted the need to carefully consider the metabolic effects of statin use when evaluating its risk–benefit ratio for diabetic individuals [62]. However, these findings are in stark contrast to the beneficial effects of statins in the treatment of NAFLD. Future research efforts are expected to provide more information on whether prolonged statin use may yield more detrimental than advantageous outcomes.

3.3. From Lab to Liver: The Promising Future of Developing New Drugs for NAFLD

More recently, new potential drugs for NAFLD have been studied. The most common treatment targets are the farnesoid X receptor (FXR), a nuclear receptor, and obeticholic acid (OCA), which is a synthetically modified analogue of chenodeoxycholic acid [63]. These agents improve insulin resistance, regulate glucose and lipid metabolism, and have anti-inflammatory and anti-fibrotic effects in NAFLD [64]. Yonoussi et al. observed that 308 patients who received OCA 25 mg daily had an improvement in fibrosis, compared to the control group [65]. Interestingly, the multicenter, randomized, placebo-controlled FLINT trial documented that those who responded to OCA, defined as patients with a ≥30% reduction in liver lipid content, had an improvement in the histological features of NASH, including fibrosis and steatosis as well as reduced cell death [66]. However, one of the limitations of OCA use is that it can increase serum LDL levels. Therefore, the safety of the combination of OCA with statin in patients with NASH is being tested in ongoing studies. Non bile acid farnesoid X-activated receptor (FXR) agonists, including tropifexor, cilofexor, EDP-305, and nidufexo, have also been tested for NAFLD [67]. The main difference between OCA and cilofexor is that the latter caused a reduction in liver lipid content in patients with NASH without altering blood levels of lipids or indicators of insulin resistance [68]. An anti-inflammatory drug, the stearoyl-CoA desaturase (SCD) 1 inhibitor, plays a key role in liver lipogenesis. The main action is to catalyze the conversion of saturated fatty acids to MUFA, protecting against hepatic steatosis [69][70]. Two animal studies showed that SCD1 activity was elevated in proportion to liver lipid content in models of NAFLD and genetic knockout of hepatic SCD1 expression effectively reduced fatty liver and insulin resistance in animals fed a high-fat diet [71][72]. Recently, a clinical trial revealed a reduction in liver fat content, resolution of NASH, and improvement of liver fibrosis in individuals with NAFLD and prediabetes or T2DM after the use of aramchol [73]. Given that to date there is no FDA-approved therapy for the treatment of NAFLD, evaluating the efficacy and safety profile of new agents is of paramount importance. However, the fact that liver biochemistry does not always reflect hepatic histology makes the conduction of biopsy studies important, which on the other hand, present significant technical challenges for obvious reasons.

Table 1 presents ongoing trials investigating the safety and efficacy of new medications for the treatment of NAFLD.

Table 1. Ongoing trials of new medications for the treatment of NAFLD.

Drug	Trial Identifier	Number of Patients	Mechanism	T2DM Inclusion Criteria	Primary Endpoint
Elafibranor	NCT02704403	2000	PPARα/δ dual agonist	T2DM only with HbA1c ≤ 9%	% of patients with NASH resolution without fibrosis worsening at week 72 from BL, long term liver-related outcomes
Saroglitazar	NCT04193982	250	PPAR-α/γ agonist	NA	Change in NFS at week 8, 16, and 24
Obeticholic Acid	NCT03439254	919	FXR agonist	T2DM only with HbA1c ≤ 9.5%	% of patients with improvement of liver fibrosis by ≥1 stage with no worsening of NASH after 18 months
Obeticholic Acid	NCT02548351	2480	FXR agonist	T2DM only with HbA1c ≤ 9.5%	Improvement of liver fibrosis by ≥1stage with no worsening of NASH OR achieving NASH resolution without worsening of liver fibrosis at month 18 from BL, long term liver-related outcomes
Cenicriviroc	NCT03028740	2000	CCR2/5 dual antagonist	T2DM with HbA1c ≤ 10%	Improvement of liver fibrosis by ≥1 stage with no worsening of NASH after 12 months, long term liver-related outcomes
Aramchol	NCT04104321	2000	SCD1 inhibitor	T2DM with controlled glycemia or prediabetes	NASH resolution with no worsening of fibrosis OR fibrosis improvement by ≥1 stage with no worsening of NASH at week 52 from BL, Long term liver-related outcomes
Resmetirom	NCT03900429	2000	THR-β agonist	T2DM with HbA1c < 9%	NASH resolution in patients with F2-F3 fibrosis after 52 weeks, long term liver-related outcomes

BL: baseline, CCR2/5: C-C chemokine receptors type 2 and type 5, FXR: farnesoid X receptor, HbA1c: glycated hemoglobin, LXR: liver X receptor, NA: data not available, NAFLD: non-alcoholic fatty liver disease, NFS: NAFLD fibrosis score, PPAR: peroxisome proliferator-activated receptor, NASH: non-alcoholic steatohepatitis, SCD: stearoyl-CoA desaturase, SGLT: sodium-glucose cotransporter, THR: thyroid hormone receptor, T2DM: type 2 diabetes.

3.4. Effects of Anti-Obesity Drugs

During recent years, weight loss pharmacotherapy has been an attractive option for patients with NAFLD, with or without T2DM and with a BMI > 30 kg/m^2 or >27 kg/m^2 in the presence of at least one metabolic comorbidity, because it can lead to the remission of diabetes and improves the progression of fatty liver disease [70][73]. The US Food and Drug Administration (FDA) has approved six medications for chronic weight management: orlistat, lorcaserin, phentermine/topiramate, bupropion/noltrexone, liraglutide and semaglutide that are associated with a decrease in body weight of at least 5% in one year [73]. Interestingly, a closer look at the literature reveals that, except for the long-term effects on glycemic control, orlistat selectively reduces visceral fat and prevents the digestion of free fatty acids that are responsible for the increase in liver and peripheral insulin resistance [74]. In 2005, a meta-analysis of seven randomized control trials showed that patients who received 120 mg orlistat three times received an average weight loss of 3.8 kg compared to 1.4 kg in the placebo group after 12 weeks [75]. In contrast, no data are available on the effects of topiramate, naltrexone, bupropion, and phentermine on liver outcomes in patients with NAFLD [76].

References

1. Preiss, D.; Sattar, N. Non-alcoholic fatty liver disease: An overview of prevalence, diagnosis, pathogenesis and treatme nt considerations. Clin. Sci. 2008, 115, 141–150.
2. Waxman, A. WHO’s global strategy on diet, physical activity and health: Response to a worldwide epidemic of non-com municable diseases. Scand. J. Nutr./Naringsforsk. 2004, 48, 58–60.
3. Perseghin, G.; Lattuada, G.; De Cobelli, F.; Ragogna, F.; Ntali, G.; Esposito, A.; Belloni, E.; Canu, T.; Terruzzi, I.; Scifo, P.; et al. Habitual Physical Activity Is Associated With Intrahepatic Fat Content in Humans. Diabetes Care 2007, 30, 683

–688.

4. George, A.; Bauman, A.; Johnston, A.; Farrell, G.; Chey, T.; George, J. Independent effects of physical activity in patient s with nonalcoholic fatty liver disease. Hepatology 2009, 50, 68–76.
5. Oh, S.; So, R.; Shida, T.; Matsuo, T.; Kim, B.; Akiyama, K.; Isobe, T.; Okamoto, Y.; Tanaka, K.; Shoda, J. High-Intensity Aerobic Exercise Improves Both Hepatic Fat Content and Stiffness in Sedentary Obese Men with Nonalcoholic Fatty Li ver Disease. Sci. Rep. 2017, 7, srep43029.
6. Zhang, H.-J.; Pan, L.-L.; Ma, Z.-M.; Chen, Z.; Huang, Z.-F.; Sun, Q.; Lu, Y.; Han, C.-K.; Lin, M.-Z.; Li, X.-J.; et al. Long-t erm effect of exercise on improving fatty liver and cardiovascular risk factors in obese adults: A 1-year follow-up study. Diabetes Obes. Metab. 2016, 19, 284–289.
7. Jakovljevic, D.G.; Hallsworth, K.; Zalewski, P.; Thoma, C.; Klawe, J.J.; Day, C.P.; Newton, J.; Trenell, M.I. Resistance e xercise improves autonomic regulation at rest and haemodynamic response to exercise in non-alcoholic fatty liver dise ase. Clin. Sci. 2013, 125, 143–149.
8. Pennisi, G.; Celsa, C.; Spatola, F.; Dallio, M.; Federico, A.; Petta, S. Pharmacological Therapy of Non-Alcoholic Fatty Li ver Disease: What Drugs Are Available Now and Future Perspectives. Int. J. Environ. Public Health 2019, 16, 4334.
9. Golabi, P.; Locklear, C.T.; Austin, P.; Afdhal, S.; Byrns, M.; Gerber, L.; Younossi, Z.M. Effectiveness of exercise in hepati c fat mobilization in non-alcoholic fatty liver disease: Systematic review. World J. Gastroenterol. 2016, 22, 6318–6327.
10. Lee, I.M.; Shiroma, E.J.; Lobelo, F.; Puska, P.; Blair, S.N.; Katzmarzyk, P.T.; Lancet Physical Activity Series Working Gr oup. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. Lancet 2012, 380, 219–229.
11. Petroni, M.L.; Brodosi, L.; Bugianesi, E.; Marchesini, G. Management of non-alcoholic fatty liver disease. BMJ 2021, 37 2, m4747.
12. Romero-Gómez, M.; Zelber-Sagi, S.; Trenell, M. Treatment of NAFLD with diet, physical activity and exercise. J. Hepat ol. 2017, 67, 829–846.
13. Chalasani, N.; Younossi, Z.; LaVine, J.E.; Charlton, M.; Cusi, K.; Rinella, M.; Harrison, S.A.; Brunt, E.M.; Sanyal, A.J. T he diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018, 67, 328–357.
14. Glen, J.; Floros, L.; Day, C.; Pryke, R. Non-alcoholic fatty liver disease (NAFLD): Summary of NICE guidance. BMJ 201 6, 354, i4428.
15. Anderson, R.M.; Weindruch, R. Metabolic reprogramming, caloric restriction and aging. Trends Endocrinol. Metab. 201 0, 21, 134–141.
16. Ludwig, D.S.; Ebbeling, C.B. The Carbohydrate-Insulin Model of Obesity: Beyond “Calories In, Calories Out”. JAMA Int ern. Med. 2018, 178, 1098–1103.
17. Holmer, M.; Lindqvist, C.; Petersson, S.; Moshtaghi-Svensson, J.; Tillander, V.; Brismar, T.B.; Hagström, H.; Stål, P. Tre atment of NAFLD with intermittent calorie restriction or low-carb high-fat diet—A randomised controlled trial. JHEP Rep. 2021, 3, 100256.
18. Vilar-Gomez, E.; Martinez-Perez, Y.; Calzadilla-Bertot, L.; Torres-Gonzalez, A.; Gra-Oramas, B.; Gonzalez-Fabian, L.; F riedman, S.L.; Diago, M.; Romero-Gomez, M. Weight Loss Through Lifestyle Modification Significantly Reduces Featur es of Nonalcoholic Steatohepatitis. Gastroenterology 2015, 149, 367–378.e5.
19. Kirk, E.; Reeds, D.N.; Finck, B.N.; Mayurranjan, M.S.; Patterson, B.W.; Klein, S. Dietary Fat and Carbohydrates Differe ntially Alter Insulin Sensitivity During Caloric Restriction. Gastroenterology 2009, 136, 1552–1560.
20. Mantovani, A.; Petracca, G.; Csermely, A.; Beatrice, G.; Targher, G. Sodium-Glucose Cotransporter-2 Inhibitors for Trea tment of Nonalcoholic Fatty Liver Disease: A Meta-Analysis of Randomized Controlled Trials. Metabolites 2020, 11, 22.
21. Musso, G.; Gambino, R.; De Michieli, F.; Cassader, M.; Rizzetto, M.; Durazzo, M.; Fagà, E.; Silli, B.; Pagano, G. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 200 3, 37, 909–916.
22. Perdomo, C.M.; Frühbeck, G.; Escalada, J. Impact of Nutritional Changes on Nonalcoholic Fatty Liver Disease. Nutrien ts 2019, 11, 677.
23. Abdelmalek, M.F.; Suzuki, A.; Guy, C.; Unalp-Arida, A.; Colvin, R.; Johnson, R.J.; Diehl, A.M.; Nonalcoholic Steatohepat itis Clinical Research Network. Increased fructose consumption is associated with fibrosis severity in patients with nona lcoholic fatty liver disease. Hepatology 2010, 51, 1961–1971.
24. Gupta, V.; Mah, X.-J.; Garcia, M.C.; Antonypillai, C.; Van Der Poorten, D. Oily fish, coffee and walnuts: Dietary treatmen t for nonalcoholic fatty liver disease. World J. Gastroenterol. 2015, 21, 10621–10635.

25. Halima, B.H.; Sarra, K.; Houda, B.J.; Sonia, G.; Abdallah, A. Antidiabetic and Antioxidant Effects of Apple Cider Vinegar on Normal and Streptozotocin-Induced Diabetic Rats. Int. J. Vitam. Nutr. Res. 2018, 88, 223–233.

26. Fushimi, T.; Suruga, K.; Oshima, Y.; Fukiharu, M.; Tsukamoto, Y.; Goda, T. Dietary acetic acid reduces serum cholesterol and triacylglycerols in rats fed a cholesterol-rich diet. Br. J. Nutr. 2006, 95, 916–924.

27. Shishehbor, F.; Mansoori, A.; Sarkaki, A.; Jalali, M.; Latifi, S. Apple Cider Vinegar Attenuates Lipid Profile in Normal and Diabetic Rats. Pak. J. Biol. Sci. 2008, 11, 2634–2638.

28. Hadi, A.; Pourmasoumi, M.; Najafgholizadeh, A.; Clark, C.C.T.; Esmaillzadeh, A. The effect of apple cider vinegar on lipid profiles and glycemic parameters: A systematic review and meta-analysis of randomized clinical trials. BMC Complement. Med. Ther. 2021, 21, 179.

29. Ousaaid, D.; Laaroussi, H.; Bakour, M.; ElGhouizi, A.; Aboulghazi, A.; Lyoussi, B.; Elarabi, I. Beneficial Effects of Apple Vinegar on Hyperglycemia and Hyperlipidemia in Hypercaloric-Fed Rats. J. Diabetes Res. 2020, 2020, 9284987.

30. Brunt, E.M.; Wong, V.W.S.; Nobili, V.; Day, C.P.; Sookoian, S.; Maher, J.J.; Bugianesi, E.; Sirlin, C.B.; Neuschwander-Tetri, B.A.; Rinella, M.E. Nonalcoholic fatty liver disease. Nat. Rev. Dis. Prim. 2015, 1, 15080.

31. Jiang, X.; Zheng, J.; Zhang, S.; Wang, B.; Wu, C.; Guo, X. Advances in the Involvement of Gut Microbiota in Pathophysiology of NAFLD. Front. Med. 2020, 7, 361.

32. Burguera, B.; Agusti, A.; Arner, P.; Baltasar, A.; Barbe, F.; Barcelo, A.; Breton, I.; Cabanes, T.; Casanueva, F.F.; Couce, M.E.; et al. Critical assessment of the current guidelines for the management and treatment of morbidly obese patients. J. Endocrinol. Investig. 2007, 30, 844–852.

33. Nguyen, N.T.; Varela, J.E. Bariatric surgery for obesity and metabolic disorders: State of the art. Nat. Rev. Gastroenterol. Hepatol. 2016, 14, 160–169.

34. Alghamdi, S.; Mirghani, H.; Alhazmi, K.; Alatawi, A.M.; Brnawi, H.; Alrasheed, T.; Badoghaish, W. Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy effects on obesity comorbidities: A systematic review and meta-analysis. Front. Surg. 2022, 9, 953804.

35. Seeras, K.; Lopez, P.P. Sleeve Gastrectomy; Starpearls Pubilshing: Treasure Island, FL, USA, 2021.

36. Lee, Y.; Doumouras, A.G.; Yu, J.; Brar, K.; Banfield, L.; Gmora, S.; Anvari, M.; Hong, D. Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis. Clin. Gastroenterol. Hepatol. 2019, 17, 1040–1060.e11.

37. Schwenger, K.J.; Fischer, S.E.; Jackson, T.; Okrainec, A.; Allard, J.P. In nonalcoholic fatty liver disease, Roux-en-Y gastric bypass improves liver histology while persistent disease is associated with lower improvements in waist circumference and glycemic control. Surg. Obes. Relat. Dis. 2018, 14, 1233–1239.

38. Weiner, R. Surgical Treatment of Non-Alcoholic Steatohepatitis and Non-Alcoholic Fatty Liver Disease. Dig. Dis. 2010, 28, 274–279.

39. Mantovani, A.; Byrne, C.; Scorletti, E.; Mantzoros, C.; Targher, G. Efficacy and safety of anti-hyperglycaemic drugs in patients with non-alcoholic fatty liver disease with or without diabetes: An updated systematic review of randomized controlled trials. Diabetes Metab. 2020, 46, 427–441.

40. Kalavalapalli, S.; Bril, F.; Guingab, J.; Vergara, A.; Garrett, T.J.; Sunny, E.N.; Cusi, K. Impact of exenatide on mitochondrial lipid metabolism in mice with nonalcoholic steatohepatitis. J. Endocrinol. 2019, 241, 293–305.

41. Katsiki, N.; Perakakis, N.; Mantzoros, C. Effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Ex quo et quo vadimus? Metabolism 2019, 98, 3–9.

42. Mayerson, A.B.; Hundal, R.S.; Dufour, S.; Lebon, V.; Befroy, D.; Cline, G.W.; Enocksson, S.; Inzucchi, S.E.; Shulman, G.I.; Petersen, K.F. The Effects of Rosiglitazone on Insulin Sensitivity, Lipolysis, and Hepatic and Skeletal Muscle Triglyceride Content in Patients With Type 2 Diabetes. Diabetes 2002, 51, 797–802.

43. Dos Coelho, F.S.; Borges-Canha, M.; von Hafe, M.; Neves, J.S.; Vale, C.; Leite, A.R.; Carvalho, D.; Leite-Moreira, A. Effects of sodium-glucose co-transporter 2 inhibitors on liver parameters and steatosis: A meta-analysis of randomized clinical trials. Diabetes Metab. Res. Rev. 2021, 37, e3413.

44. Shibuya, T.; Fushimi, N.; Kawai, M.; Yoshida, Y.; Hachiya, H.; Ito, S.; Kawai, H.; Ohashi, N.; Mori, A. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: A prospective randomized controlled pilot study. Diabetes Obes. Metab. 2017, 20, 438–442.

45. Eriksson, J.W.; Lundkvist, P.; Jansson, P.-A.; Johansson, L.; Kvarnström, M.; Moris, L.; Miliotis, T.; Forsberg, G.-B.; Risérus, U.; Lind, L.; et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: A double-blind randomised placebo-controlled study. Diabetologia 2018, 61, 1923–1934.

46. Sattar, N.; Fitchett, D.; Hantel, S.; George, J.T.; Zinman, B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: Results from randomised trials including the EMPA-REG OUTCOME® trial. Diabetologia 2018, 61, 2155–2163.

47. Gross, B.; Pawlak, M.; Lefebvre, P.; Staels, B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. Nat. Rev. Endocrinol. 2017, 13, 36–49.

48. Belfort, R.; Harrison, S.A.; Brown, K.; Darland, C.; Finch, J.; Hardies, J.; Balas, B.; Gastaldelli, A.; Tio, F.; Pulcini, J.; et al. A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis. N. Engl. J. Med. 2006, 355, 2297–2307.

49. Boettcher, E.; Csako, G.; Pucino, F.; Wesley, R.; Loomba, R. Meta-analysis: Pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Aliment. Pharmacol. Ther. 2011, 35, 66–75.

50. Al-Mrabeh, A.; Hollingsworth, K.G.; Shaw, J.A.M.; McConnachie, A.; Sattar, N.; Lean, M.E.J.; Taylor, R. 2-year remission of type 2 diabetes and pancreas morphology: A post-hoc analysis of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2020, 8, 939–948.

51. Thomas, M.K.; Nikooienejad, A.; Bray, R.; Cui, X.; Wilson, J.; Duffin, K.; Milicevic, Z.; Haupt, A.; Robins, A.D. Dual GIP and GLP-1 Receptor Agonist Tirzepatide Improves Beta-cell Function and Insulin Sensitivity in Type 2 Diabetes. J. Clin. Endocrinol. Metab. 2020, 106, 388–396.

52. Saeedi, P.; Petersohn, I.; Salpea, P.; Malanda, B.; Karuranga, S.; Unwin, N.; Colagiuri, S.; Guariguata, L.; Motala, A.A.; Ogurtsova, K.; et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res. Clin. Pract. 2019, 157, 107843.

53. Jeon, Y.; Son, K.Y. Effects of different definitions of low muscle mass on its association with metabolic syndrome in older adults: A Korean nationwide study. Geriatr. Gerontol. Int. 2021, 21, 1003–1009.

54. Pose, E.; Trebicka, J.; Mookerjee, R.P.; Angeli, P.; Ginès, P. Statins: Old drugs as new therapy for liver diseases? J. Hepatol. 2019, 70, 194–202.

55. Dongiovanni, P.; Petta, S.; Mannisto, V.; Mancina, R.M.; Pipitone, R.; Karja, V.; Maggioni, M.; Kakela, P.; Wiklund, O.; Mozzi, E.; et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. J. Hepatol. 2015, 63, 705–712.

56. Lee, J.; Lee, H.W.; Lee, K.S.; Lee, H.S.; Park, J.Y. Effects of Statin Use on the Development and Progression of Nonalcoholic Fatty Liver Disease: A Nationwide Nested Case-Control Study. Am. J. Gastroenterol. 2021, 116, 116–124.

57. Nakade, Y.; Murotani, K.; Inoue, T.; Kobayashi, Y.; Yamamoto, T.; Ishii, N.; Ohashi, T.; Ito, K.; Fukuzawa, Y.; Yoneda, M. Ezetimibe for the treatment of non-alcoholic fatty liver disease: A meta-analysis. Hepatol. Res. 2017, 47, 1417–1428.

58. Dewidar, B.; Kahl, S.; Pafili, K.; Roden, M. Metabolic liver disease in diabetes—From mechanisms to clinical trials. Metabolism 2020, 111, 154299.

59. Lee, C.-H.; Fu, Y.; Yang, S.-J.; Chi, C.-C. Effects of Omega-3 Polyunsaturated Fatty Acid Supplementation on Non-Alcoholic Fatty Liver: A Systematic Review and Meta-Analysis. Nutrients 2020, 12, 2769.

60. Valenzuela, R.; Videla, L.A. Impact of the Co-Administration of N-3 Fatty Acids and Olive Oil Components in Preclinical Nonalcoholic Fatty Liver Disease Models: A Mechanistic View. Nutrients 2020, 12, 499.

61. Huang, T.; Wu, T.; Wu, Y.; Li, X.; Tan, J.; Shen, C.; Xiong, S.; Feng, Z.; Gao, S.; Li, H.; et al. Long-term statins administration exacerbates diabetic nephropathy via ectopic fat deposition in diabetic mice. Nat. Commun. 2023, 14, 390.

62. Mansi, I.A.; Chansard, M.; Lingvay, I.; Zhang, S.; Halm, E.A.; Alvarez, C.A. Association of Statin Therapy Initiation With Diabetes Progression: A Retrospective Matched-Cohort Study. JAMA Intern. Med. 2021, 181, 1562–1574.

63. Cariou, B.; Byrne, C.D.; Loomba, R.; Sanyal, A.J. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. Diabetes Obes. Metab. 2021, 23, 1069–1083.

64. Kong, B.; Luyendyk, J.P.; Tawfik, O.; Guo, G.L. Farnesoid X Receptor Deficiency Induces Nonalcoholic Steatohepatitis in Low-Density Lipoprotein Receptor-Knockout Mice Fed a High-Fat Diet. Experiment 2008, 328, 116–122.

65. Younossi, Z.M.; Ratziu, V.; Loomba, R.; Rinella, M.; Anstee, Q.M.; Goodman, Z.; Bedossa, P.; Geier, A.; Beckebaum, S.; Newsome, P.N.; et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: Interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019, 394, 2184–2196.

66. Neuschwander-Tetri, B.A.; Loomba, R.; Sanyal, A.J.; Lavine, J.E.; Van Natta, M.L.; Abdelmalek, M.F.; Chalasani, N.; Dasarathy, S.; Diehl, A.M.; Hameed, B.; et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): A multicentre, randomised, placebo-controlled trial. Lancet 2015, 385, 956–965.

67. Friedman, S.L.; Neuschwander-Tetri, B.A.; Rinella, M.; Sanyal, A.J. Mechanisms of NAFLD development and therapeutic strategies. Nat. Med. 2018, 24, 908–922.

68. Miyazaki, M.; Flowers, M.T.; Sampath, H.; Chu, K.; Otzelberger, C.; Liu, X.; Ntambi, J.M. Hepatic stearoyl-CoA desatura se-1 deficiency protects mice from carbohydrate-induced adiposity and hepatic steatosis. Cell Metab. 2007, 6, 484–49 6.

69. One-Year Results of the Global Phase 2b Randomized Placebo-Controlled ARREST Trial of Aramchol, a Stearoyl CoA Desaturasemodulator in NASH Patients. Available online: https://www.natap.org/2018/AASLD/AASLD_222.htm (access ed on 1 November 2018).

70. Garvey, W.T.; Mechanick, J.I.; Brett, E.M.; Garber, A.J.; Hurley, D.L.; Jastreboff, A.M.; Nadolsky, K.; Pessah-Pollack, R.; Plodkowski, R. American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr. Pract. 2016, 22 (Suppl. 3), 1–203.

71. Kotronen, A.; Seppänen-Laakso, T.; Westerbacka, J.; Kiviluoto, T.; Arola, J.; Ruskeepää, A.L.; Matej, O.; Hannele, Y.-J. Hepatic stearoyl-CoA desaturase (SCD)-1 activity and diacylglycerol but not ceramide concentrations are increased in t he nonalcoholic human fatty liver. Diabetes 2009, 58, 203–208.

72. Gutiérrez-Juárez, R.; Pocai, A.; Mulas, C.; Ono, H.; Bhanot, S.; Monia, B.P.; Rossetti, L. Critical role of stearoyl-CoA de saturase-1 (SCD1) in the onset of diet-induced hepatic insulin resistance. J. Clin. Investig. 2006, 116, 1686–1695.

73. Khera, R.; Murad, M.H.; Chandar, A.K.; Dulai, P.S.; Wang, Z.; Prokop, L.J.; Loomba, R.; Camilleri, M.; Singh, S. Associ ation of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Met a-analysis. JAMA 2016, 315, 2424–2434.

74. Damci, T.; Yalin, S.; Balci, H.; Osar, Z.; Korugan, U.; Ozyazar, M.; Ilkova, H. Orlistat augments postprandial increases in glucagon-like peptide 1 in obese type 2 diabetic patients. Diabetes Care 2004, 27, 1077–1080.

75. Ruof, J.; Golay, A.; Berne, C.; Collin, C.; Lentz, J.; Maetzel, A. Orlistat in responding obese type 2 diabetic patients: Met a-analysis findings and cost-effectiveness as rationales for reimbursement in Sweden and Switzerland. Int. J. Obes. 20 05, 29, 517–523.

76. Pan, C.S.; Stanley, T.L. Effect of Weight Loss Medications on Hepatic Steatosis and Steatohepatitis: A Systematic Revi ew. Front. Endocrinol. 2020, 11, 70.