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TOPIC HIGHLIGHT

2015 Advances in Nonalcoholic Fatty Liver Disease

Management of non-alcoholic fatty liver disease in 2015

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Abstract

There is no single pharmacologic therapy that has been approved to treat nonalcoholic fatty liver disease in the general population. The backbone of therapy currently includes intensive lifestyle modification with established targets for diet and weight loss. The use of unsweetened, unfiltered coffee along with limiting high fructose corn syrup have emerged as beneficial dietary recommendations. The use of empiric oral hypoglycemic agents and vitamin E, however, has not been widely accepted. Developing bariatric surgical techniques are promising, but additional studies with long-term follow up are needed before it can be widely recommended. Finally, liver transplantation is an increasingly frequent consideration once complications of end-stage disease have developed. The future treatment of those with nonalcoholic fatty liver disease will likely involve a personalized approach. The importance of the gut microbiome in mediating hepatocyte inflammation and intestinal permeability is emerging and may offer avenues for novel treatment. The study of anti-fibrotic agents such as pentoxifylline and FXR agonists hold promise and new pathways, such as hepatocyte cannabinoid receptor antagonists are being studied. With the incidence of obesity and the metabolic syndrome increasing throughout the developed world, the future will continue to focus on finding novel agents and new applications of existing therapies to help prevent and to mediate the progression of nonalcoholic fatty liver disease.

Key words: Lobular inflammation; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Liver fibrosis

Core tip: Lifestyle modification with diet and exercise remain the mainstay of therapy for nonalcoholic fatty liver disease. Loss of at least 7%-10% of body weight with limiting high fructose corn syrup and high-saturated/high glycemic index foods should be combined with regular, vigorous physical activity. The future of treatment will continue to evolve and likely include the role of anti fibrotic agents, surgical management and transplantation when indicated.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a form of chronic hepatitis that affects a wide range of individuals. It is estimated that up to 95 million adults in the United States have been affected and that the prevalence will continue to increase[1]. The most common documented comorbidities that have been associated with NAFLD include obesity, impaired insulin sensitivity and dyslipidemia. There is growing evidence that there is also a connection to a number of other disorders including obstructive sleep apnea, hypothyroidism, hypopituitarism, hypogonadism and polycystic ovarian syndrome[2].

NAFLD exists as a spectrum and is best characterized histologically. Important features include steatosis, inflammation, hepatocellular ballooning and fibrosis. NAFLD can be classified as non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). In NAFL hepatocellular injury is absent, whereas NASH involves the presence of inflammation with hepatocyte damage, with or without fibrosis[2]. Once present, these specific changes mediate the risk of future disease progression.

The importance of treatment for NAFLD comes from the knowledge of its complications. It is well established that patients with NASH can progress to develop cirrhosis and its complications[2] including hepatocellular carcinoma (HCC)[2]. However, the most common cause of death in patients with NAFLD is cardiovascular disease. Today, the medical community continues to look for evidence-based therapy to improve liver histology and reduce associated risks. These include lifestyle management with a goal of sustained weight loss, treating associated features of the metabolic syndrome to reduce cardiovascular risk, as well as liver specific pharmacologic therapy and in some cases transplantation. As we look beyond 2015, we are hopeful that studies currently evaluating the role of the microbiome, novel insulin sensitizers and anti-fibrotic agents will provide effective therapies for this condition. We aim to discuss the current management of NAFLD and future directions of treatment.

LIFESTYLE MODIFICATION: EXERCISE

Based on the 2012 published practice guidelines, lifestyle intervention has shown to improve hepatic aminotransferases along with steatosis[2]. It broadly encompasses both dietary changes and regular exercise. One of the objective end points for many studies has included the NAFLD activity score (NAS), which was validated by the NASH Clinical Research Network[3]. The components are based on histologic examination and include hepatic steatosis, lobular inflammation and hepatocyte ballooning. A randomized study by Promrat *et al*[3] showed that there was a significant improvement in the NAS score in those treated with lifestyle modification. It required subjects to achieve 7%-10% reduction in body weight by limiting caloric intake and completing moderate intensity activities for 200 min/wk. They also included regular support with behavior modification and dieticians for meal planning. Unfortunately, this study failed to identify a significant difference in fibrosis on biopsy[3]. Although specific targets exist for weight loss, sustained results over the long-term are the backbone for continued success. Even alone, there has been improvement seen with exercise without dietary modification[2].

We now know that the intensity of physical activity can effect the histologic improvements demonstrated in patients. Those with vigorous activity had decreased odds of NASH and lower glucose and insulin values[4]. It can be quantified as 75 min/wk with activities that include running on a treadmill or using a step machine. Doubling the time was shown to provide additional benefits of reduced NASH activity[4].

LIFESTYLE MODIFICATION: DIET

Dietary composition has been scrutinized as a possible modifiable factor in altering the course of NAFLD development and progression. As the North American diet continues to evolve, so does the need for finding easy meal options to keep up with a fast paced lifestyle. That often leads to consumption of high caloric, processed foods and carbonated beverages. Magnetic resonance spectroscopy (MRS) has been helpful to quantify the accumulation of fat in the liver. The cut off in NAFLD is based on intrahepatic triglyceride (IHTG) content and set at greater than 5.6%[5]. Fructose, trans-fatty acids and saturated fat may contribute to increased IHTG, while poly and mono-unsaturated fats may play a protective role[5]. The result is an imbalance of free fatty output from the liver. Saturated fats have been especially shown to contribute toward the development of cardiovascular disease, type 2 diabetes mellitus and the metabolic syndrome[6]. Although they have also been shown to increase the IHTG, studies of high calorie diets may have other potential cofounders to explain the results[7]. Trans-fatty acids are unsaturated and produced due to hydrogenation. They have at least one double bond in the trans configuration and are found in many processed food items. Their role in humans and NAFLD has not been well described at this time[5]. Polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids have been shown to regulate expression of proteins involved with fatty acid oxidation[8]. As a result, this may lead to an overall improvement in the IHTG content in the liver[5].

The monosaccharide fructose and its disaccharide form, sucrose are primary dietary sweeteners that are highly lipogenic sugars[9]. This has lead to examine

fructose and its role in NAFLD. Intake of sucrose and high fructose corn syrup has increased 1000% over the past 40 years and can account for up to 10% of caloric food intake[10]. Overall, fructose is a component of insulin resistance and a contributor to visceral adiposity and plasma triglycerides[9]. The downstream effect is fat deposition in the liver in excess amounts. Steatosis is the eventual result of the liver's inability to keep up with synthesis, utilization and expenditure of fat[9]. A cross sectional analysis by Vos *et al*[9] showed that daily consumption of fructose was associated with significantly more fibrosis (OR = 2.6, P = 0.004) and significantly lower plasma high density lipoprotein (HDL) (P < 0.001). More studies will be needed to further determine how fructose contributes to NAFLD development and progression to NASH and how this can be mediated[9]. Overall, a balanced diet consisting of lower glycemic index fruits and vegetables, low saturated fats along with whole grains has been shown to reduce liver fat on MRS[1].

The effect of coffee has been previously studied in other causes of liver disease, including HCC. A recent meta-analysis by Bravi *et al*[11] revealed a significant decrease in relative risk for HCC with increasing coffee consumption. Similarly in NAFLD, a study by Molloy *et al*[12] looked at caffeine and coffee intake. There appeared to be an inverse relationship between regular unsweetened, unfiltered caffeinated coffee consumption and hepatic fibrosis[12]. This effect could not be extrapolated to other types of caffeine. Unfortunately, there have been no prospective trials identifying a specific amount required for achieve maximal benefit. Although the exact ingredient responsible for these benefits is unknown, it has been postulated that it due to the reduced amount of cafestol and kahweol in unfiltered coffee. These are diterpene molecules that are thought to have anti-inflammatory properties, but also potentially increase serum cholesterol. By filtering coffee, it may prevent an elevation in low-density lipoprotein cholesterol and serve as a reasonable adjunct to therapy in NAFLD patients[13].

PHARMACOLOGIC THERAPY

Given the related pathophysiology of NAFLD and associated metabolic comorbidities, it has been hoped that the pharmacologic treatment of these conditions could lead to an improvement in liver histology. This has lead to numerous clinical trials, although none have demonstrated significant benefit to be approved as liver-specific therapy[3].

Poly unsaturated fatty acids have been shown to reduce insulin resistance, lipid production and systemic inflammation. The n-3 form of PUFAs represent the family of omega 3 fatty acids. The physiologic forms exist as eicosapentanoic acid (EPA) along with docosahexanoic acid and are significantly decreased in NASH[14]. Therefore, supplementation with the synthetic ethyl-EPA (EPA-E) that is found in many fish oil preparations was studied by Sanyal *et al*[14]. Twelve months of therapy was compared to placebo by Sanyal *et al*[14]. During the trial, up to 25% of patients dropped out, mainly due to side effects including nausea, diarrhea and abdominal discomfort[14]. Using histologic improvement as a primary endpoint, there was unfortunately no significant effect on steatosis or fibrosis stage when comparing placebo with lower (1800 mg/d) or higher (2700 mg/d) doses of of EPA-E[14].

The evaluation of insulin sensitizing agents in NAFLD has mainly focused on the role metformin and the family of thiazolidinedione. While pioglitazone has shown improvement in steatosis and inflammation in non diabetics, there are safety concerns including bladder cancer risk, weight gain, fractures and heart failure[2]. The PIVENS study was a multicenter, randomized, placebo-controlled trial published in 2010. In nondiabetic and non-cirrhotic adults with biopsy proven NASH there was a decrease in fibrosis after 96 wk (P = 0.04, NNT = 6.9), but it did not meet the pre-specified statistical endpoint[15]. The lack of significance might be attributed to the fact that 28% of the initial biopsy specimens lacked hepatocellular ballooning in the pioglitazone group compared to 17% in the placebo group[15]. As result, it would be harder to meet the targets set in the primary outcome, including improvement in hepatocellular ballooning and fibrosis score.

Metformin is widely used as a first line agent to control blood sugar and its role in NAFLD has been studied. In a recent systematic review and meta-analysis there was an improvement in aminotransferases, but no significant histologic response was identified[16]. In contrast, a small randomized controlled trial published by Bugianesi *et al*[17] showed a decrease in liver fat, necroinflammation and fibrosis in nondiabetic adults treated with metformin. Further to this, metformin's effect on overall mortality was examined in a cohort study of DM patients who developed NASH related cirrhosis, with a 57% reduced risk of death and no evidence of lactic acidosis in those taking metformin[18]. Although current guidelines do not recommend metformin as a specific treatment for liver disease in patients with NASH, it may be a useful adjunct in management of associated DM[2].

Vitamin E is a well-known antioxidant that prevents the propagation of free radicals. This was also examined in the PIVENS trial with a dose of 800 IU/d over 96 wk[15]. Overall, there was a significant improvement in the primary endpoint of hepatocellular ballooning and steatosis (P = 0.001, NNT = 4.2)[15]. This occurred without significant improvement in fibrosis score[15]. Vitamin E is not free from adverse effects, with associations including risk of hemorrhagic stroke, prostate cancer and all-cause mortality. As such, physicians must be mindful in using it, and when patients are placed on vitamin E to treat NASH, its efficacy should be assessed after 6 to 12 mo of therapy[15]. The current recommendations advocate for use of Vitamin E in nondiabetic patients with biopsy proven NASH[2].

Angiotensin-converting enzyme inhibitors (ACE-I)

and angiotensin receptor blockers (ARBs) are important renin-angiotensin-aldosterone system (RAAS) modulators used in treating hypertension and proteinuria. There is also evidence that these agents help with overall insulin sensitivity in DM patients[19]. A meta-analysis by Al-Mallah *et al*[20] established that there was a 20% reduction in the incidence of new onset DM with the use of ACE-I and ARBs. The mechanism behind this may be through vasodilation and improved blood flow to the pancreas, promoting insulin secretion and delivery to tissues[19]. Studies for the role of the RAAS in NAFLD are ongoing. Animal models have shown a down regulation in pro-inflammatory and pro-fibrotic cytokines, leading to prevention of lobular inflammation along with hepatic fibrosis[21]. In humans, studies have largely looked at the role for ARBs only. A study by Georgescu *et al*[22] determined that Telmisartan improved transaminase levels and insulin resistance more than Valsartan. Only Telmisartan, however, showed a significant decrease in NAS activity score and fibrosis[22].

LIVER TRANSPLANTATION

End stage disease leads to consideration of liver transplantation in applicable patients. A meta-analysis looking at this issue found that NASH patients had equivalent survival compare to those who were transplanted for other causes[23]. Although it can be successful, transplantation in this patient population also carries with it significant risk. When compared to other etiologies for liver transplantation, death in subjects with underlying NASH was more likely due to cardiovascular events (OR = 1.65) and sepsis (OR = 1.71)[23]. This should emphasize the importance of modifying underlying risk factors. With the increase in the obesity epidemic in the developed world, NAFLD is projected to become the leading cause of liver transplantation in the near future[24]. Given the limited resources for transplantation, the need for effective therapies to prevent end-stage liver disease is all the more important.

FUTURE MANAGEMENT

An area of significant interest and study in the treatment of NAFLD is bariatric surgery. Interventions include gastric bypass, gastric banding and sleeve gastrectomy[2]. Early on, weight loss goals could be achieved with use of bariatric surgery as an adjuvant treatment to lifestyle modification. The reduced gastric remnant works to decrease hunger and stimulate satiety[25]. In addition to loss of central adiposity in subcutaneous tissues, it could also lead to a decrease fat deposition in the liver. Prospective data is mixed and indicates an improvement in steatosis and hepatocyte ballooning in NAFL[2]. Reversal of NASH with fibrosis, however, is less clear and appears more resistant[25]. As a result, current guidelines have not indicated that bariatric surgery should be used a specific treatment of NASH at this time.

An evolving area of interest in NAFLD pathogenesis and management involves the gut microbiome. Its role is complex and at present, incompletely understood. Resident microbiota consist of millions of microbial genes that influence metabolism, physiology and gene regulation[26]. They aid in synthesis of vitamins, digestion of fibers and prevention of pathogen colonization[27]. As such, the role in intestinal disorders such as C difficile infection, inflammatory bowel disease and irritable bowel syndrome is increasingly recognized[26]. It is thought that the microbiome's role in NAFLD may be mediated *via* the development of endotoxins involved in obesity and insulin resistance. The major fermentation products of microbiota are short chain fatty acids (SCFAs)[27]. There is also an association with increased production of SCFAs in overweight and obese subjects when compared to lean individuals[28]. The pathophysiology is thought to be due to an increased ability to harvest energy through the glucagon-like peptide 2 receptor[27]. The resident species of bacteria in the gut that are involved in these complex interactions is also important to consider. A study in obese patients by Ley *et al*[29] showed that the proportion of specific microbacteria (Bacteroidetes) was lower in obese compared to lean patients. This proportion subsequently increased with weight loss[29].

During digestion, bacterial metabolites are presented to the liver through the portal vein[27]. This allows exposure of gut-derived factors from the small intestine to potentially cause a downstream inflammatory response in liver tissue[1]. Interestingly, SCFAs may also play a protective role with down-regulating insulin signaling in adipose tissue through G-protein couple receptor 43[27]. The future of the gut microbiome is exciting and may one day lead to a personalized approach to manage NAFLD. This is a promising development for possible future pharmacologic applications in NAFLD.

There are a wide range of additional pharmacologic agents currently under study. Endocannabinoid CB1 receptors expressed on hepatocytes and myofibroblasts are contributors to hepatic fat storage[1]. Peripheral receptor antagonists could prove to be a beneficial strategy in this patient population. Additional newer oral hypoglycemic agents GLP-1 receptor analogues (Exenatide™) and DPP-4 inhibitors (Sitagliptin™) may play an indirect role through glycemic control. In patients with NAFLD and DM, Exenatide™ has been shown to improve body weight and decrease transaminases[1]. In addition, Sitagliptin™ decreases liver triglyceride content[1]. Pentoxifylline has been shown to decrease free-radical induced oxidative stress and inhibit lipid oxidation[1]. A meta-analysis of randomized double-blind controlled trials by Zeng *et al*[30] examined the application of pentoxifylline in NAFLD. Not only were there a decrease in aminotransferases, but also significant improvement in steatosis, lobular inflammation and fibrosis[30], suggesting this may become a potential treatment option[31].

Obeticholic acid is a bile acid derivative that may have a future role in non-cirrhotic NASH patients. Bile acids bind to Farnesoid X nuclear receptors to promote

insulin sensitivity and decrease hepatic gluconeogenesis along with circulating triglycerides[32]. A recent multi-center randomized controlled trial by Neuschwander-Tetri *et al*[33] showed a significant improvement in NAS score and fibrosis when compared to placebo (P = 0.0002). These derivatives also inhibit conversion of cholesterol to bile acids, which resulted in an increase in total cholesterol/low density lipoprotein along with decrease in HDL[33]. The clinical significance of this needs further exploration before recommendations can be made for its use.

Wolfberry, or Lycii fructus, is a well-known drug supplement in traditional Chinese medicine. Another common supplement now in North America is epigallocatechin-3-gallate (pure green tea extract). The premise behind their potential beneficial effect relies on reduction of oxidative stress and inflammation within hepatocytes. The endpoint would be less downstream damage within the liver. Xiao *et al*[34] noted that rat models showed an improvement in fat accumulation, fibrosis and eventual histology. The key molecules include many pro-inflammatory cytokines including interleukin molecules. Both of these supplements also mediate inflammation by regulating nuclear factor kappa B, which many chemokine signaling pathways depend on. The application in human models is ongoing.

CONCLUSION

There is currently no single pharmacologic or surgical therapy that has been shown to be universally effective in all patients with NAFLD. Histologic regression presently hinges on lifestyle modification through diet and exercise with the goal of improvement in weight as well as the detection and management of associated metabolic disorders. As such, caloric restriction along with regular exercise should be considered in all patients. The use of unfiltered, unsweetened coffee, reduction of ingestion of fructose and saturated fats are reasonable specific dietary recommendations for patients. Use of vitamin E should be restricted to non-diabetic patients with biopsy proven NASH and the use of oral hypoglycemic agents (*i.e.,* Pioglitazone) in nondiabetics should be considered on an individual patient basis. In patients with DM metformin is a reasonable first line agent. Statins have been proven to be safe in this population and given the increased cardiovascular mortality in NAFLD, should be used as indicated for management of hyperlipidemia.

Although not yet widely recommended, the use of surgical techniques including bariatric surgery may aid in weight loss and contribute to improved insulin resistance and hepatic fat deposition in carefully selected patients. Transplantation is an option for end stage disease in some individuals. Underlying cardiovascular disease is still a concern for post transplant mortality and recurrence of NAFLD is common if underlying behaviors and risk factors are not addressed. Promising targets for future management include bile acid transport, the gut microbiome, pro-inflammatory and liver fibrosis pathways. We have come a long way, but still have to advocate for aggressive management of risk factors to prevent progression of NAFLD and potential impact on healthcare resources.

REFERENCES

1 **Federico A**, Zulli C, de Sio I, Del Prete A, Dallio M, Masarone M, Loguercio C. Focus on emerging drugs for the treatment of patients with non-alcoholic fatty liver disease. *World J Gastroenterol* 2014; **20**: 16841-16857 [PMID: 25492998 DOI: 10.3748/wjg.v20.i45.16841]

2 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]

3 **Promrat K**, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, Fava JL, Wing RR. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 121-129 [PMID: 19827166 DOI: 10.1002/hep.23276]

4 **Kistler KD**, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. *Am J Gastroenterol* 2011; **106**: 460-468; quiz 469 [PMID: 21206486 DOI: 10.1038/ajg.2010.488]

5 **Sullivan S**. Implications of diet on nonalcoholic fatty liver disease. *Curr Opin Gastroenterol* 2010; **26**: 160-164 [PMID: 20010099 DOI: 10.1097/MOG.0b013e3283358a58]

6 **Funaki M**. Saturated fatty acids and insulin resistance. *J Med Invest* 2009; **56**: 88-92 [PMID: 19763019 DOI: 10.2152/jmi.56.88]

7 **Kechagias S**, Ernersson A, Dahlqvist O, Lundberg P, Lindström T, Nystrom FH. Fast-food-based hyper-alimentation can induce rapid and profound elevation of serum alanine aminotransferase in healthy subjects. *Gut* 2008; **57**: 649-654 [PMID: 18276725 DOI: 10.1136/gut.2007.131797]

8 **Clarke SD**. Nonalcoholic steatosis and steatohepatitis. I. Molecular mechanism for polyunsaturated fatty acid regulation of gene transcription. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G865-G869 [PMID: 11557505]

9 **Vos MB**, Lavine JE. Dietary fructose in nonalcoholic fatty liver disease. *Hepatology* 2013; **57**: 2525-2531 [PMID: 23390127 DOI: 10.1002/hep.26299]

10 **Abdelmalek MF**, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, Diehl AM. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 1961-1971 [PMID: 20301112 DOI: 10.1002/hep.23535]

11 **Bravi F**, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 1413-1421.e1 [PMID: 23660416 DOI: 10.1016/j.cgh.2013.04.039]

12 **Molloy JW**, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology* 2012; **55**: 429-436 [PMID: 21987293 DOI: 10.1002/hep.24731]

13 **Torres DM**, Harrison SA. Is it time to write a prescription for coffee? Coffee and liver disease. *Gastroenterology* 2013; **144**: 670-672 [PMID: 23453671 DOI: 10.1053/j.gastro.2013.02.015]

14 **Sanyal AJ**, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology* 2014; **147**: 377-384.e1 [PMID: 24818764 DOI: 10.1053/j.gastro.2014.04.046]

15 **Sanyal AJ**, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]

16 **Li Y**, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Biomed Rep* 2013; **1**: 57-64 [PMID: 24648894 DOI: 10.3892/br.2018.18]

17 **Bugianesi E**, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, David E, Rizzetto M, Marchesini G. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol* 2005; **100**: 1082-1090 [PMID: 15842582 DOI: 10.1111/j.1572-0241.2005.41583.x]

18 **Zhang X**, Harmsen WS, Mettler TA, Kim WR, Roberts RO, Therneau TM, Roberts LR, Chaiteerakij R. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology* 2014; **60**: 2008-2016 [PMID: 24798175 DOI: 10.1002/hep.27199]

19 **Paschos P**, Tziomalos K. Nonalcoholic fatty liver disease and the renin-angiotensin system: Implications for treatment. *World J Hepatol* 2012; **4**: 327-331 [PMID: 23355909 DOI: 10.4254/wjh.v4.i12.327]

20 **Al-Mallah M**, Khawaja O, Sinno M, Alzohaili O, Samra AB. Do angiotensin converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis. *Cardiol J* 2010; **17**: 448-456 [PMID: 20865674]

21 **Warner FJ**, Lubel JS, McCaughan GW, Angus PW. Liver fibrosis: a balance of ACEs? *Clin Sci* (Lond) 2007; **113**: 109-118 [PMID: 17600527 DOI: 10.1042/CS20070026]

22 **Georgescu EF**, Ionescu R, Niculescu M, Mogoanta L, Vancica L. Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. *World J Gastroenterol* 2009; **15**: 942-954 [PMID: 19248193 DOI: 10.3748/wjg.15.942]

23 **Wang X**, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 394-402.e1 [PMID: 24076414 DOI: 10.1016/j.cgh.2013.09.023]

24 **Charlton MR**, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249-1253 [PMID: 21726509 DOI: 10.1053/j.gastro.2011.06.061]

25 **Caiazzo R**, Lassailly G, Leteurtre E, Baud G, Verkindt H, Raverdy V, Buob D, Pigeyre M, Mathurin P, Pattou F. Roux-en-Y gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. *Ann Surg* 2014; **260**: 893-898; discussion 898-899 [PMID: 25379859 DOI: 10.1097/SLA.0000000000000945]

26 **Kinross JM**, von Roon AC, Holmes E, Darzi A, Nicholson JK. The human gut microbiome: implications for future health care. *Curr Gastroenterol Rep* 2008; **10**: 396-403 [PMID: 18627653 DOI: 10.1186/gm228]

27 **Zhu L**, Baker RD, Baker SS. Gut microbiome and nonalcoholic fatty liver diseases. *Pediatr Res* 2015; **77**: 245-251 [PMID: 25310763 DOI: 10.1038/pr.2014.157]

28 **Schwiertz A**, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* (Silver Spring) 2010; **18**: 190-195 [PMID: 19498350 DOI: 10.1038/oby.2009.167]

29 **Ley RE**, Turnbaugah PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; **444**: 1022-1023 [PMID: 17183309]

30 **Zeng T**, Zhang CL, Zhao XL, Xie KQ. Pentoxifylline for the treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized double-blind, placebo-controlled studies. *Eur J Gastroenterol Hepatol* 2014; **26**: 646-653 [PMID: 24743504 DOI: 10.1097/MEG.0000000000000068]

31 **Du J**, Ma YY, Yu CH, Li YM. Effects of pentoxifylline on non-alcoholic fatty liver disease: a meta-analysis. *World J Gastroenterol* 2014; **20**: 569-577 [PMID: 24574727 DOI: 10.3748/wjg.v20.i2.569]

32 **Porez G**, Prawitt J, Gross B, Staels B. Bile acid receptors as targets for the treatment of dyslipidemia and cardiovascular disease. *J Lipid Res* 2012; **53**: 1723-1737 [PMID: 22550135 DOI: 10.1194/jlr.R024794]

33 **Neuschwander-Tetri BA**, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, Chalasani N, Dasarathy S, Diehl AM, Hameed B, Kowdley KV, McCullough A, Terrault N, Clark JM, Tonascia J, Brunt EM, Kleiner DE, Doo E. 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 [PMID: 25468160 DOI: 10.1016/S0140-6736(14)61933-4]

34 **Xiao J**, Fai So K, Liong EC, Tipoe GL. Recent advances in the herbal treatment of non-alcoholic Fatty liver disease. *J Tradit Complement Med* 2013; **3**: 88-94 [PMID: 24716162 DOI: 10.4103/2225-4110.110411]

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