Chapter 7

Nutrition and Lifestyle Modifications in the Prevention and Treatment of Non-Alcoholic Fatty Liver Disease

Kingsley Asare Kwadwo Pereko, Jacob Setorglo, Matilda Steiner-Asiedu and Joyce Bayebanona Maaweh Tiweh

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71368

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a burgeoning health problem worldwide. NAFLD is an umbrella term for a range of liver conditions affecting people who drink little to no alcohol Different methods are employed in the diagnosis of NAFLD. Certain drugs, genetics, lifestyle factors have been implicated in the development of NAFLD. NAFLD symptoms are asymptomatic but indicated when there is unexplained persistent elevation of liver enzyme levels. Nutrition and lifestyle modifications are widely prescribed as helpful in the prevention and treatment of Non-Alcoholic Fatty Liver disease (NAFLD). Dietary and lifestyle modifications are apparent measures considering the disease association with obesity, diabetes, and cardiovascular disease which many reviews have linked to the condition. Reduction in body weight, involvement in both aerobic and anaerobic exercises, conscious intake in the types of fat and carbohydrates are helpful in the management of NAFLD. This chapter highlights the various theories and principles underlying nutrition and lifestyle modifications in the prevention and treatment of NAFLDs.

Keywords: fatty liver, obesity, non-alcoholic, dietary, lifestyle

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a burgeoning health problem worldwide and is a risk factor for both hepatic and cardiometabolic mortality [1, 2]. A meta-analysis of prevalence, incidence and outcome of NAFLD following publications on pubmed from 1989 to 2015 estimated global prevalence at 25.24% (95% CI: 22.10–28.65) with highest prevalence in

the Middle East 31.79% (13.48–58.23) and South America 30.45% (22.74–39.44) and lowest in Africa 13.48% (5.69–28.69) [2]. NAFLD describes a range of conditions caused by a build-up of fat within liver cells and can be divided into four stages namely:

1. Simple fatty liver (hepatic steatosis). Under normal conditions, very little fat is stored in liver cells of humans. Hepatic steatosis therefore refers to a situation where excess fat accumulates in the hepatic cells. Sometimes simple fatty liver does not cause any harm to the liver or pose health risks. However, in some instances it leads to NAFLD and its severe forms and that is where the problem arises.
2. Non-alcoholic steatohepatitis (NASH). This expression is much less common than NAFLD. Here, the excess fat stored in the liver cells is associated with inflammation of the liver.
3. Fibrosis: This is associated with persistent hepatitis, including steatohepatitis and may lead to scarring of the liver tissue (fibrosis). This is not life threatening since when fibrosis some of the liver cells that continue to perform its functions.
4. Cirrhosis: This stage of a liver disease can be life threatening because normal liver tissues are replaced by a lot of fibrosis. The structure and function of the liver are therefore modified. There are different scientific means of detecting liver diseases.

2. Diagnosis

There are different methods of diagnosing NAFLD. The test ranges from metabolic syndrome assessment, detecting metabolites in the blood as well as enzymes such as Alanine transaminase (ALT) and Aspartate Aminotransferase (AST) [3]. Medical imaging and sonographic techniques are also performed to create an image of the liver. Further tests such as fibroscan and biopsy may be conducted apart from those listed earlier to determine the stage of the liver disease [4].

3. Risk factors

A wide range of diseases and conditions can predispose one to non-alcoholic fatty liver disease (NAFLD). Non-alcoholic steatohepatitis expresses itself among some sub-populations such as older people, diabetics and the obese. Certain drugs and hepatitis have been implicated in the development of NAFLD as well. Some risks are usually from lifestyle origin. These include:

- High cholesterol and triglycerides levels,
- Metabolic syndrome,

http://dx.doi.org/10.5772/intechopen.71368

- Central adiposity,
- Polycystic ovary syndrome,
- Sleep apnea,
- Genetics,
- Hypothyroidism,
- Hypopituitarism [5].

Nutritional factors have also been cited as risks in the development of the disease. These include rapid weight loss, total parenteral nutrition, starvation and protein-calorie malnutrition [6]. The most common risk factor associated with NAFLD is the presence of the metabolic syndrome. The metabolic syndrome is defined by the presence of 3 or more of the following criteria (**Table 1**): (1) increased waist circumference, (2) hypertriglyceridemia, (3) hypertension, (4) high fasting glucose, and (5) a low high-density lipoprotein (HDL) level.

Parameter*	Value
Impaired glucose tolerance	Fasting blood glucose level ≥ 110 mg/dL
High blood pressure	≥130/85 mm Hg
Elevated triglyceride levels	>250 mg/dL
Low high-density lipoprotein level	<40 mg/dL for men; <50 mg/dL for women
Abdominal obesity	Waist: >102 cm (40 inches) for men; >88 cm (35 inches) for women

*Metabolic syndrome is diagnosed by the presence of 2 or more of these parameters.
Source: [2].

Table 1. Diagnostic criteria for metabolic syndrome.

4. Signs and symptoms and management

Nonalcoholic fatty liver disease occurs in every age group but especially in people in their 40s and 50s. The condition is also closely linked to metabolic syndrome, which is a cluster of abnormalities including increased abdominal fat, poor ability to use the hormone insulin, high blood pressure and high blood levels of triglycerides. NAFLD symptoms are asymptomatic but indicated when there is unexplained persistent elevation of liver enzyme levels after hepatitis and other chronic liver diseases have been excluded. However, at certain stages of the disease, patients are malaise, fatigue, and right upper quadrant or diffuse abdominal discomfort. Hepatomegaly is found on clinical examination. When there is cirrhosis there may be; spider angiomata, ascites, splenomegaly, hard liver border, ascites, portal hypertension and jaundice or pruritus [7].

Clinical evaluation includes a careful history and physical examination. It is relevant to inquire about excess alcohol consumption which is defined as intakes greater than 30 g/day for men and greater than 20 g/day for women within the past 5 years. A drink is 350 mL (12 oz) of beer, 120 mL (4 oz) of wine, and 45 mL (1.5 oz) of hard liquor each contain 10 g of alcohol.

There are several approaches to managing NAFLD. Hepatoprotective therapy, antioxidants insulin-sensitizing agents and treatment of obesity are part of these. However, this text limits itself to the nutritional management of the NAFLD. Key to nutritional therapeutic procedures are lifestyle changes in diet and improving exercise habits in addition to the control of comorbidities which are secondary to the development of NAFLD [8]. For instance, bile acid derivatives and associated compounds that influence bile acid related are becoming prominent therapeutic agents for NAFLD [9, 10, 11]. The immediate associated lifestyle causes of NAFLD are targeted in the management of the disease condition.

5. Obesity and genetics

Obesity when combined with physical inactivity and genetic predisposition, has been directly associated with metabolic syndrome and NAFLD among some adult populations [12, 2]. Obesity itself is the failure of normal homeostatic regulation of energy utilization [9]. NAFLD can be a precursor to developing metabolic syndrome or insulin resistance [10]. Data suggest that about 80% of adults who are class 1 and/or 2 obese and 90% morbid obese according to the World Health Organization classification are at risk of having NAFLD [13]. Body weight loss can alter the cellular activity of adipose tissue and reverse many of the negative consequences of NAFLD. The excess fat and energy content of a meal has been associated with NAFLD development in healthy populations [14, 15]. Insulin resistance, oxidative stress, and cytokine toxicity results due to obesity and these factors have been implicated in the pathogenesis of NAFLD [16]. Among these factors, central adiposity and insulin resistance have direct association with hepatic fat content and visceral adiposity [17–19]. Polymorphisms (genetic variations) in the single-nucleotide polymorphisms (SNPs) T455C and C482T in APOC3 are associated with fatty liver disease. The carriers of T-455C, C-482 T, or both (not additive) had a 30% increase in fasting plasma apolipoprotein C3, 60% increase in fasting plasma triglyceride and 46% reduction in plasma triglyceride clearance. Oxidative stress, hormonal imbalances, and mitochondrial abnormalities can be potential causes.

6. Total fat

Dietary composition of a meal in terms of the macro-molecule distribution has a positive relation with the development of NAFLD. The amount and type of dietary fat may directly affect liver fat content, with high-fat diets being potentially harmful [20]. It has also been shown that a high ratio of omega-6 to omega-3 polyunsaturated fatty acids (PUFAs) and an increased

http://dx.doi.org/10.5772/intechopen.71368

intake of saturated and trans fatty acids are associated with NAFLD [21–23]. It was noted that when severely obese patients were fed diets containing higher percentage of total fat beyond recommended ranges, the risk of developing NALFD increased [24]. The deduction therefore was that the type of fat ingested rather than the amount is associated with NAFLD in obese individuals.

7. Saturated fatty acids

Saturated fatty acid component in meals has been shown to induce insulin resistance especially among the obese [25–27]. In epidemiologic studies, both total fat and saturated fat in the diet had significant correlation with triglyceride content in hepatic cells [28, 29]. In a double-blind randomized controlled trial of two reduced-fat diets, compared with a control diet both reduced-fat diets decreased amount of low density lipoprotein cholesterol (LDLc) in healthy males [30]. There was a decrease in high density lipoprotein cholesterol (HDLc) and increase in triglyceride levels increased with the reduced-fat diets. The authors concluded that reduced saturated fat intake (below 10%) may benefit patients with NAFLD. It was also observed that, low total fat and low saturated fat diet (23% fat and 7% saturated fat) predicted changes in HDLc and LDLc but not the amount of fat in the hepatocytes [31].

8. *Trans* fatty acids

Trans fatty acids are positively associated with an increase in inflammatory processes, plasma triglycerides, and cholesterol as well as a reduction in HDLc level [32, 33]. Animal studies have shown positive relationships between the increased consumption of trans fatty acids from oxidized oils and liver inflammation [34, 35].

9. Polyunsaturated fatty acids (PUFAs)

Essential fatty acid, Omega-3 (which is a type of polyunsaturated fatty acids) PUFA levels are decreased in the hepatic tissue of people with NAFLD [22, 36] A higher omega-6 to omega-3 PUFA ratio may contribute to the development of a fatty liver within the hepatocytes of people NAFLD [36].

10. High carbohydrate intake

High carbohydrate intake especially the amount and type of carbohydrate consumed have an important impact on the development of NAFLD [37]. Simple carbohydrates intakes can lead to the development of NAFLD [38]. Meals high in carbohydrates lead to increased

amounts of circulating insulin, which contribute to elevated triglyceride concentrations even under isocaloric conditions [39, 40]. A higher carbohydrate intake more than the recommended daily values has been positively associated with liver inflammation and NAFLD [24].

Coupled with a low-fat meal, high-carbohydrate meal promotes the development of a NAFLD through increased de novo fatty acid and triglyceride synthesis [41].

11. High-fructose corn syrup intake

Epidemiological data suggest that dietary pattern and an increased intake of simple sugars, especially fructose is associated with the development of NAFLD [42, 43]. The link is not too clear although it is assumed that the carbohydrates components increased risk of fatty infiltration of the liver or muscle. Therefore it was hypothesized that the link is through both indirect and direct mechanisms [44, 45]. Indirect association manifest itself through the adverse metabolic effects that can increase the risk of developing NAFLD. Fructose may cause hepatotoxic damage as a form of direct route link with NAFLD. Studies [46–49] have suggested that increased fructose consumption augments fat mass, de novo lipogenesis, and inflammation. There is also induction of insulin resistance and fasting and postprandial triglycerides, which in turn, can result in liver steatosis. In other studies [50, 51], sugar-sweetened beverage consumption was found to be associated with fatty liver independent of body mass index of the individuals. Direct positive association was found between the amount of fructose consumed and the development of NAFLD [52, 53]. Age and frequency of consuming fructose-based food was also found to be related to liver inflammation and NAFLD [54].

12. Physical inactivity

Physical activity has been documented to improve health and hence the World Health Organization recommendations for aerobic an anaerobic exercises across the life span. Physical inactivity however, has been associated with NAFLD. Using matched controls for age and gender, only about one-fifth of individuals with NAFLD met recommendations for physical activity [55, 56]. Among 349 individuals studied, the NAFLD group engaged in less physical activity, including total, aerobic, and resistance [55].

It has been noted that decreased physical activity correlates with intra-hepatic fat, decreased cellular insulin sensitivity, and increased central adiposity [57, 58]. Sedentary time alone is associated with metabolic status. Sedentary times predicted higher levels of fasting insulin, independent of the amount of time spent engaging in moderate- or vigorous-intensity activity [59]. Therefore to improve metabolic health it is generally important to reduce sedentary lifestyle even when one meets the requirements for physical activity.

http://dx.doi.org/10.5772/intechopen.71368

13. Treatments

Aggressive pursuit of modified lifestyle modifications coupled with dietary changes are critical in treating NAFLD when body weight is the underlying cause. That is because dietary macronutrient composition, physical activity, and all play critical roles in successful weight reduction. Weight loss is effective for improving NAFLD as it positively influences insulin sensitivity and dyslipidemia.

14. Body weight loss

It was found that about 9% body weight loss significantly improves NAFLD [60]. The result was thought to be due to improvements in inflammation and steatosis. Reduction in body weight through lowering of daily caloric intake of about 200 kcal/day improved liver cellular structure histology and enzymes function. A 10% body weight reduction resulted in a 45% reduction in liver fat content [61]. Lifestyle modification through dietary intake, exercise, and behavior modification with the guidelines from health experts has been show to lead to resolution in NALFD [62]. A weight reduction of about 7% was therefore recommended [63]. A combination of diet and exercise reduces fibrosis and amount of liver fat by an average of 40% [64–66]. The degree of hepatic fat reduction is related to the intensity of the lifestyle mediation and normally required a weight loss range of 5–10% is suggested.

15. Bariatric surgery

Among persons with higher grades of obesity, physical remedy such as reduction in dietary intake and physical activities does not result in resolution of NAFLD. Other means such as bariatric surgery is the most effective strategy to achieve and maintain weight loss [67]. Results from several uncontrolled studies [68–70] and controlled studies [71, 72] indicated that body weight loss achieved through bariatric surgery reduces amount of liver enzymes and improves NAFLD.

A study found an association between bariatric surgery and lower serum alanine transferase and aspartate aminotransferase levels at two and 10 years follow-up [73] and histological improvements [74]. Steatosis, steatohepatitis, and fibrosis improved among majority of patients that have undergone surgery [75]. It is worth noting that hepatic decompensation can occur after gastric bypass so decision to opt for this should be taken with great care [3].

16. Nutrient content and healthful fats

Dietary composition can directly manipulate NAFLD progress. Changing either the composition of the macronutrient or micronutrient content can directly affect the level of inflammation,

amount of serum lipids and insulin resistance [49]. Inverse association was found between Mediterranean diet consumption and cardiovascular disease risk [76]. Among obese women and overweight men, a low-fat diet decreased hepatic fat compared with a high-fat diet [64, 77]. The dietary recommendation is that the diet contain less than 7% saturated fats, less than 1% of trans fats and 25–35% of the calorific intake should be total fat among which is polyunsaturated fatty acid.

17. Monounsaturated fats

It was found that replacing carbohydrate intake with monounsaturated fatty acids (MUFAs) to about 32 g/day increases triglyceride-rich lipoprotein catabolism [30]. This can lead to resolution of NAFLD. This finding is supported by epidemiological studies [31, 78]. Olive oil which contains about 73% MUFAs appears to provide a direct benefit in improving plasma lipids and possible NAFLD [79]. In randomized trials, [80, 81] isocaloric low-fat/high-carbohydrate diet improved hepatic fat and improved insulin sensitivity. The diet was composed of 50% MUFAs and 18% omega-3 PUFAs, 40% from carbohydrate, and 20% protein. These findings were independent of body weight loss of patients.

18. Omega-3 Omega-6 PUFAs

Evidence from epidemiologic and randomized controlled trials indicate that supplementation with omega-3 PUFAs lowers triglyceride levels and reduces the risk of coronary heart disease and mortality.94,95 High consumption of omega-3 PUFAs derived from fish diminishes hepatic triglyceride lipoprotein secretion and inhibits de novo lipogenesis. [82]. Using the Therapeutic Lifestyle Change diet criteria with a diet high in fish-derived omega-3 fatty acid (1.23 g/day EPA + DHA) vs. a low fish diet (0.27 g/day EPA + DHA) for 24 weeks, the higher fish diet decreased plasma triglycerides by 24%. Three human clinical trials support these findings by showing that giving patients with NAFLD omega-3 PUFAs (1 to 2.7 g/day for six to 12 months) improved hepatic steatosis, inflammation, and fibrosis [82, 83]. Capanni and Spadaro both demonstrated that triglyceride levels decreased 25 to 37 mg/dL when patients' diets were supplemented with 1 to 2 g of omega-3 PUFAs per day for six and 12 months, respectively. This was thought to be through diminishes hepatic triglyceride lipoprotein secretion and inhibition de novo lipogenesis [82–84]. Diets based on therapeutic lifestyle change criteria supports improvements in NAFLD as the diet improves liver steatosis, inflammation, and fibrosis [85]. In a non-controlled trial, omega-6 PUFAs (15% of energy as linoleic acid) reduced liver fat compared with a diet high in saturated fatty acids in abdominally obese patients [86]. A diet consisting of mainly reduced simple carbohydrate may confer similar benefits among NALFD patients [87, 88].

http://dx.doi.org/10.5772/intechopen.71368

19. Low sugar intake

Diet designed to produce a caloric deficit of 500 to1000 kcal/day is advised. Reduction of dietary carbohydrates, in particular dietary fructose, is the most beneficial and has been found to improve the lipid profile in overweight patients. Diets with less carbohydrate and more fat have relatively greater benefits in NAFLD management [89, 90]. Hypocaloric diet made up from 40% carbohydrate and 45% fat decreased serum alanine transaminase concentration than did a higher-carbohydrate (60%), low-fat diet (25% fat) [91]. Low-carbohydrate caloric restriction significantly improved hepatic insulin sensitivity. Diets with less carbohydrate and more fat have relatively greater benefits for insulin levels, triglycerides, and HDL cholesterol concentrations than do hypocaloric, low-fat diets. A hypocaloric diet moderately lower in carbohydrate (40% carbohydrate and 45% fat) decreased serum alanine transaminase concentrations to a greater degree than did a higher-carbohydrate, low-fat diet (60% carbohydrate and 25% fat).106 For individuals with NAFLD who were glucose intolerant, the low-carbohydrate caloric restriction significantly improved hepatic insulin sensitivity compared with the low-fat diet. In contrast, changes in visceral fat mass and insulin sensitivity were similar between a low-calorie, reduced-carbohydrate diet (fewer than 90 g of carbohydrate) and a reduced-fat diet (less than 20% fat). The World Health Organization recommends that the daily intake of added sugars makes up no more than 10% of total energy. The American Heart Association recommends limiting the amount of added sugars to no more than one-half of daily discretionary calories, which for women is approximately 100 kcal/day (6 tsp. of sugar) and for men is 150 kcal/day (9 tsp. of sugar).

20. Physical activity therapy

Physical activity enhances insulin sensitivity and favorably modifies lipids independent of weight loss [92, 93] Data suggest that there is improvement in cellular liver characteristics when NALFD individuals become active [94]. Exercise can lead to improvement in insulin sensitivity which intends contributes to the fatty acid delivery to the liver [95]. Improvement in insulin resistance and may decrease hepatic steatosis, inflammation, and disease progression in NAFLD [96, 97]. Four studies have investigated the effects of exercise without dietary modification on hepatic steatosis. Exercise can independently results in reduction in the fat in the hepatocytes without a significant weight change [98–101].

21. Exercise intensity and duration

Both intermittent and daily exercise helps achieve weight loss and improve insulin sensitivity [102]. Intensity and duration contribute to energy expenditure and therefore can lead to insulin sensitivity, triglycerides, and serum glucose amount [103]. Vigorous exercise and doubling

the duration of vigorous exercise was associated with decreased odds of developing fat in the liver [104]. Increased exercise by 60 minutes or more per week significantly reduced body weight and all liver enzymes [105]. Regular aerobic exercise for half an hour at least per day at 60–70% max heart rate for least 5 days per week reduces liver alanine transaminase levels [106].

22. Aerobic and resistance exercises

Increased aerobic exercise has been associated with improvement in the metabolic parameters associated with NAFLD [61, 94, 106]. Combined aerobic and resistance exercises have been shown to be more effective than aerobic exercise alone for resolving inflammation and cardiovascular risk factors [107]. An intervention of 30 minutes of aerobic exercise and 20 minutes of resistance exercise three times per week was found to be associated with improvements in hepatic fat among NAFLD patients [108]. This combination activity improves hepatic insulin sensitivity [100] reduction in liver fat [109]. Both findings were independent of body weight reduction. Antioxidant treatments such as vitamins and minerals supplementation have been mentioned to decrease oxidative stress and improve oxidative injury among NAFLD patients.

23. Vitamin E

In theory, vitamin E and other vitamins called antioxidants could help protect the liver by reducing or neutralizing the damage caused by inflammation. But more research is needed. Some evidence suggests vitamin E supplements may be helpful for people with liver damage caused by nonalcoholic fatty liver disease [110]. But vitamin E has been linked with increased risk of death and, in men, an increased risk of prostate cancer. Several small trials in humans with NAFLD have supported an effect of tocopherol (vitamin E) on the improvement of transaminase levels but there have been discordant results in histologic improvement [111]. There was a significant improvement in hepatic steatosis with vitamin E intakes at levels of 800 to 1000 IU/day [112, 113] Higher intakes of the vitamin can be fatal in most cases [114, 115].

24. Vitamin D

Vitamin D may play an important role in modifying the risk of cardio metabolic outcomes [116, 117]. Serum 25-hydroxy vitamin D concentrations were correlated with NAFLD in terms of liver steatosis, inflammation and fibrosis [118].

25. EPA + DHA

The evidence supporting the use of omega-3 PUFAs for treating NAFLD have consisted of small sample sizes and laden with errors [118, 119].

26. Probiotics

Gut microbiota has been associated with the development of obesity-related NAFLD [120]. Probiotics may improve liver enzymes and decrease markers of lipid peroxidation [121, 122]. The use of prebiotics and probiotics is to modify the microbiota as preventive or therapeutic strategies [123]. Their beneficial effects on NAFLD have been limited human studies [124]. Consuming a tablet containing 500 million *Lactobacillus bulgaricus* and *Streptococcus thermophilus* for 3 months improved levels of liver enzyme in patients with NAFLD [124].

27. Other nutrients

Ginger (*Zingiber officinale*) can improve insulin sensitivity and reduce hepatic fat content [125]. In studies of people with non-alcoholic fatty liver disease, those who reported drinking coffee had less liver damage than those who drank little or no coffee. It's not clear how coffee may influence liver damage or how much coffee you'd need to drink in order to benefit. **Table 2** summarizes the nutritional guidelines in the management and treatment of NAFLD.

Weight loss	10% of initial body weight over 6 months Maintenance of weight loss Bariatric surgery when individuals qualify
Calorie intake	1200 to 1500 daily **Energy deficit of 500 kcal/day based on Mifflin-St Jeor formula*
Total fat	≤ 35% of total calories
Monounsaturated fatty acids	15–25% of total calories
Polyunsaturated fatty acids	5–10% of total calories Omega-3 fatty acids
Saturated fatty acids	7–10% of total calories
Carbohydrate	50% of total calories > 50% carbohydrate sources from whole grains Avoid high-fructose corn syrup Added sugars <10% of total calories
Protein	15% of total calories Lean and vegetable protein
Antioxidants	None
Physical activity	≥ 150 minutes/week at moderate intensity or ≥75 minutes/week at vigorous intensity Cardiovascular exercise five times weekly Resistance training two or more times weekly Decrease time spent sedentary

Source: [65, 81, 83].

Table 2. Guidelines in the management and treatment of NAFLD.

Author details

Kingsley Asare Kwadwo Pereko[1]*, Jacob Setorglo[2], Matilda Steiner-Asiedu[3] and Joyce Bayebanona Maaweh Tiweh[4]

*Address all correspondence to: kpereko@gmail.com

1 School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana

2 School of Allied Health Sciences, University of Cape Coast, Cape Coast, Ghana

3 Department of Nutrition and Food Science, University of Ghana, Legon, Ghana

4 Eye Unit, Manhyia Government Hospital, Kumasi, Ghana

References

[1] McCulough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clinics in Liver Disease. Aug 2004;**8**(3):521-533. DOI: 10.1016/j.cld.2004.04.004. PMID 15331061

[2] Chalasani N, Younossi Z, Lavine JE, et al. 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**(6):2005-2023

[3] Chalasani N et al. 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. American Journal of Gastroenterology. 2012;**107**(6):811-826

[4] Brunt EM. Pathology of non-alcoholic fatty liver disease. Nature Reviews. Gastroenterology & Hepatology. 2010;(4):195-203. Epub 2010 Mar 2

[5] Rinella ME. Nonalcoholic fatty liver disease: A systematic review. JAMA (Systematic Review). 2015;**313**(22):2263-2273. DOI: 10.1001/jama.2015.5370. PMID 26057287

[6] Allocca M, Selmi C. Emerging nutritional treatments for nonalcoholic fatty liver disease. In: Preedy VR, Lakshman R, Rajaskanthan RS, editors. Nutrition, Diet Therapy, and the Liver. Florida, USA: CRC Press; 2010. pp. 131-146. ISBN 1420085492

[7] Clark JM, Diehl AM. Nonalcoholic fatty liver disease: An underrecognized cause of cryptogenic cirrhosis. Journal of the American Medical Association. 2003;**289**(22):3000-3004. DOI: 10.1001/jama.289.22.3000. PMID 12799409

[8] Loria P, Adinolfi LE, Bellentani S, et al. Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the study of the liver (AISF) expert committee. Digestive and Liver Disease. 2010;**42**(4):272-282

[9] Dandona P, Aljada A, Bandyopadhyay A. Inflammation: The link between insulin resistance, obesity and diabetes. Trends in Immunology. 2004;**25**(1):4-7

[10] Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Järvinen H, Svegliati-Baroni G. From the metabolic syndrome to NAFLD or vice versa? Digestive and Liver Disease. 2010;**42**(5):320-330

[11] Capristo E, Miele L, Forgione A, et al. Nutritional aspects in patients with non-alcoholic steatohepatitis (NASH). European Review for Medical and Pharmacological Sciences. 2005;**9**(5):265-268

[12] Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003;**37**(4):917-923

[13] Gholam PM, Flancbaum L, Machan JT, Charney DA, Kotler DP. Nonalcoholic fatty liver disease in severely obese subjects. The American Journal of Gastroenterology. 2007;**102**(2):399-408

[14] Sobrecases H, Lê KA, Bortolotti M, et al. Effects of short-term overfeeding with fructose, fat and fructose plus fat on plasma and hepatic lipids in healthy men. Diabetes & Metabolism. 2010;**36**(3):244-246

[15] Ngo Sock ET, Le KA, Ith M, Kreis R, Boesch C, Tappy L. Effects of a short-term overfeeding with fructose or glucose in healthy young males. The British Journal of Nutrition. 2010;**103**(7):939-943

[16] Dowman JK, Tomlison JW, and Newsome PN. Pathogenesis of non-alcholic fatty liver disease. 2009;**103**:71-83 QJMed

[17] Jakobsen MU, Berentzen T, Sørensen TI, Overvad K. Abdominal obesity and fatty liver. Epidemiologic Reviews. 2007;**29**:77-87

[18] Chitturi S, Abeygunasekera S, Farrell GC, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatol. 2002;**35**(2):373-379

[19] Lee JH, Rhee PL, Lee JK, et al. Role of hyperinsulinemia and glucose intolerance in the pathogenesis of nonalcoholic fatty liver in patients with normal body weight. The Korean Journal of Internal Medicine. 1998;**13**(1):12-14

[20] Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. The Journal of Clinical Investigation. 2005;**115**(5):1343-1351

[21] Kien CL. Dietary interventions for metabolic syndrome: Role of modifying dietary fats. Current Diabetes Reports. 2009;**9**(1):43-50

[22] Spadaro L, Magliocco O, Spampinato D, et al. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. Digestive and Liver Disease. 2008;**40**(3):194-199

[23] Tanaka N, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves nonalcoholic steatohepatitis. Journal of Clinical Gastroenterology. 2008;**42**(4):413-418

[24] Solga S, Alkhuraishe AR, Clark JM, et al. Dietary composition and nonalcoholic fatty liver disease. Digestive Diseases and Sciences. 2004;**49**(10):1578-1583

[25] Lovejoy JC, Smith SR, Champagne CM, et al. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. Diabetes Care. 2002;**25**(8):1283-1288

[26] Vessby B, Uusitupa M, Hermansen K, et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. Diabetologia. 2001;**44**(3):312-319

[27] Xiao C, Giacca A, Carpentier A, Lewis GF. Differential effects of monounsaturated, polyunsaturated and saturated fat ingestion on glucose-stimulated insulin secretion, sensitivity and clearance in overweight and obese, non-diabetic humans. Diabetologia. 2006;**49**(6):1371-1379

[28] Tiikkainen M, Bergholm R, Vehkavaara S, et al. Effects of identical weight loss on body composition and features of insulin resistance in obese women with high and low liver fat content. Diabetes. 2003;**52**(3):701-707

[29] Vilar L, Oliveira CP, Faintuch J, et al. High-fat diet: A trigger of non-alcoholic steatohepatitis? Preliminary findings in obese subjects. Nutrition. 2008;**24**(11-12):1097-1102

[30] Lefevre M, Champagne CM, Tulley RT, Rood JC. Most MM. Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: Body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol. The American Journal of Clinical Nutrition. 2005;**82**(5):957-963

[31] Utzschneider KM, Bayer-Carter JL, Arbuckle MD, Tidwell JM, Richards TL, Craft S. Beneficial effect of a weight-stable, low-fat/low-saturated fat/low-glycaemic index diet to reduce liver fat in older subjects. The British Journal of Nutrition. 2013;**109**(6):1096-1104

[32] Eckel RH, Borra S, Lichtenstein AH, Yin-Piazza SY, Trans Fat Conference Planning Group. Understanding the complexity of trans fatty acid reduction in the American diet: American Heart Association trans fat conference 2006: Report of the trans fat conference planning group. Circulation. 2007;**115**(16):2231-2246

[33] Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. The American Journal of Clinical Nutrition. 2003;**77**(5):1146-1155

[34] Dhibi M, Brahmi F, Mnari A, et al. The intake of high fat diet with different trans fatty acid levels differentially induces oxidative stress and non alcoholic fatty liver disease (NAFLD) in rats. Nutrition & Metabolism (London). 2011;**8**(1):65

[35] Obara N, Fukushima K, Ueno Y, et al. Possible involvement and the mechanisms of excess trans-fatty acid consumption in severe NAFLD in mice. Journal of Hepatology. 2010;**53**(2):326-334

[36] Araya YN, Silvertown J, Gowing DJ, McConway KJ, Peter Linder H, Midgley G. A fundamental, eco-hydrological basis for niche segregation in plant communities. New Phytologist. 2011;**189**:253-258

[37] York LW, Puthalapattu S, Wu GY. Nonalcoholic fatty liver disease and low-carbohydrate diets. Annual Review of Nutrition. 2009;**29**:365-379

[38] Toshimitsu K, Matsuura B, Ohkubo I, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. Nutrition. 2007;**23**(1):46-52

[39] Garg A, Bantle JP, Henry RR, et al. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. Journal of the American Medical Association. 1994;**271**(18):1421-1428

[40] McLaughlin T, Abbasi F, Lamendola C, Yeni-Komshian H, Reaven G. Carbohydrate-induced hypertriglyceridemia: An insight into the link between plasma insulin and triglyceride concentrations. The Journal of Clinical Endocrinology and Metabolism. 2000;**85**(9):3085-3088

[41] Hudgins LC, Hellerstein M, Seidman C, Neese R, Diakun J, Hirsch J. Human fatty acid synthesis is stimulated by a eucaloric low fat, high carbohydrate diet. The Journal of Clinical Investigation. 1996;**97**(9):2081-2091

[42] Nomura K, Yamanouchi T. The role of fructose-enriched diets in mechanisms of nonalcoholic fatty liver disease. The Journal of Nutritional Biochemistry. 2012;**23**(3):203-208

[43] Alisi A, Manco M, Pezzullo M, Nobili V. Fructose at the center of necroinflammation and fibrosis in nonalcoholic steatohepatitis. Hepatology. 2011;**53**(1):372-373

[44] Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. Nature Reviews. Gastroenterology & Hepatology. 2010;**7**(5):251-264

[45] Yilmaz Y. Review article: Fructose in non-alcoholic fatty liver disease. Alimentary Pharmacology & Therapeutics. 2012;**35**(10):1135-1144

[46] Huang D, Dhawan T, Young S, Yong WH, Boros LG, Heaney AP. Fructose impairs glucose-induced hepatic triglyceride synthesis. Lipids in Health and Disease. 2011;**10**:20

[47] Koo HY, Wallig MA, Chung BH, Nara TY, Cho BH, Nakamura MT. Dietary fructose induces a wide range of genes with distinct shift in carbohydrate and lipid metabolism in fed and fasted rat liver. Biochimica et Biophysica Acta. 2008;**1782**(5):341-348

[48] Teff KL, Elliott SS, Tschöp M, et al. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. The Journal of Clinical Endocrinology and Metabolism. 2004;**89**(6):2963-2972

[49] Stanhope KL, Havel PJ. Fructose consumption: Considerations for future research on its effects on adipose distribution, lipid metabolism, and insulin sensitivity in humans. The Journal of Nutrition. 2009;**139**(6):1236S-1241S

[50] Assy N, Nasser G, Kamayse I, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. Canadian Journal of Gastroenterology. 2008;**22**(10):811-816

[51] Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. Journal of Hepatology. 2009;**51**(5):918-924

[52] Thuy S, Ladurner R, Volynets V, et al. Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1 concentrations and with fructose intake. The Journal of Nutrition. 2008;**138**(8):1452-1455

[53] Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. Journal of Hepatology. 2008;**48**(6):993-999

[54] Abdelmalek MF, Suzuki A, Guy C, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. Hepatology. 2010;**51**(6):1961-1971

[55] Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Role of leisure-time physical activity in nonalcoholic fatty liver disease: A population-based study. Hepatology. 2008;**48**(6):1791-1798

[56] Krasnoff JB, Painter PL, Wallace JP, Bass NM, Merriman RB. Health-related fitness and physical activity in patients with nonalcoholic fatty liver disease. Hepatology. 2008;**47**(4):1158-1166

[57] Perseghin G, Lattuada G, De Cobelli F, et al. Habitual physical activity is associated with intrahepatic fat content in humans. Diabetes Care. 2007;**30**(3):683-688

[58] Booth FW, Laye MJ, Lees SJ, Rector RS, Thyfault JP. Reduced physical activity and risk of chronic disease: The biology behind the consequences. European Journal of Applied Physiology. 2008;**102**(4):381-390

[59] Helmerhorst HJ, Wijndaele K, Brage S, Wareham NJ, Ekelund U. Objectively measured sedentary time may predict insulin resistance independent of moderate- and vigorous-intensity physical activity. Diabetes. 2009;**58**(8):1776-1779

[60] Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Hepatology. 2009;**49**(1):80-86

[61] Shah K, Stufflebam A, Hilton TN, Sinacore DR, Klein S, Villareal DT. Diet and exercise interventions reduce intrahepatic fat content and improve insulin sensitivity in obese older adults. Obesity (Silver Spring). 2009;**17**(12):2162-2168

[62] Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;**51**(1):121-129

[63] Wong VW, Wong GL, Choi PC, et al. Disease progression of non-alcoholic fatty liver disease: A prospective study with paired liver biopsies at 3 years. Gut. 2010;**59**(7):969-974

[64] Westerbacka J, Lammi K, Häkkinen AM, et al. Dietary fat content modifies liver fat in overweight nondiabetic subjects. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**(5):2804-2809

[65] Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of non-alcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes. 2005;**54**(3):603-608

[66] Cowin GJ, Jonsson JR, Bauer JD, et al. Magnetic resonance imaging and spectroscopy for monitoring liver steatosis. Journal of Magnetic Resonance Imaging. 2008;**28**(4):937-945

[67] Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. The New England Journal of Medicine. 2004;**351**(26):2683-2693

[68] Dixon JB, Bhathal PS, O'Brien PE. Weight loss and non-alcoholic fatty liver disease: Falls in gamma-glutamyl transferase concentrations are associated with histologic improvement. Obesity Surgery. 2006;**16**(10):1278-1286

[69] Silvestre V, Ruano M, Domínguez Y, et al. Morbid obesity and gastric bypass surgery: Biochemical profile. Obesity Surgery. 2004;**14**(9):1227-1232

[70] Stratopoulos C, Papakonstantinou A, Terzis I, et al. Changes in liver histology accompanying massive weight loss after gastroplasty for morbid obesity. Obesity Surgery. 2005;**15**(8):1154-1160

[71] Johansson HE, Haenni A, Ohrvall M, Sundbom M, Zethelius B. Alterations in proinsulin and insulin dynamics, HDL cholesterol and ALT after gastric bypass surgery. A 42-months follow-up study. Obesity Surgery. 2009;**19**(5):601-607

[72] Pontiroli AE, Pizzocri P, Librenti MC, et al. Laparoscopic adjustable gastric banding for the treatment of morbid (grade 3) obesity and its metabolic complications: A three-year study. The Journal of Clinical Endocrinology and Metabolism. 2002;**87**(8):3555-3561

[73] Burza MA, Romeo S, Kotronen A, et al. Long-term effect of bariatric surgery on liver enzymes in the Swedish obese subjects (SOS) study. PLoS One. 2013;**8**(3):e60495

[74] Hafeez S, Ahmed MH. Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: A future treatment by choice or by chance? Journal of Obesity. 2013;**2013**:839275

[75] Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: Systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2008;**6**(12):1396-1402

[76] Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. The New England Journal of Medicine. 2013;**368**(14):1279-1290

[77] van Herpen NA, Schrauwen-Hinderling VB, Schaart G, Mensink RP, Schrauwen P. Three weeks on a high-fat diet increases intrahepatic lipid accumulation and decreases metabolic flexibility in healthy overweight men. The Journal of Clinical Endocrinology and Metabolism. 2011;**96**(4):E691-E695

[78] Gillingham LG, Harris-Janz S, Jones PJ. Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. Lipids. 2011;**46**(3):209-228

[79] Alonso A, Ruiz-Gutierrez V, Martínez-González MA. Monounsaturated fatty acids, olive oil and blood pressure: Epidemiological, clinical and experimental evidence. Public Health Nutrition. 2006;**9**(2):251-257

[80] Ryan MC, Itsiopoulos C, Thodis T, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. Journal of Hepatology. 2013;**59**(1):138-143

[81] Bozzetto L, Prinster A, Annuzzi G, et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. Diabetes Care. 2012;**35**(7):1429-1435

[82] Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: Effects on risk factors, molecular pathways, and clinical events. Journal of the American College of Cardiology. 2011;**58**(20):2047-2067

[83] Grimsgaard S, Bønaa KH, Hansen JB, Myhre ES. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. The American Journal of Clinical Nutrition. 1998;**68**(1):52-59

[84] Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: A meta-analysis of randomized controlled trials. The American Journal of Medicine. 2002;**112**(4):298-304

[85] Ooi EM, Lichtenstein AH, Millar JS, et al. Effects of therapeutic lifestyle change diets high and low in dietary fish-derived FAs on lipoprotein metabolism in middle-aged and elderly subjects. Journal of Lipid Research. 2012;**53**(9):1958-1967

[86] Bjermo H, Iggman D, Kullberg J, et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: A randomized controlled trial. The American Journal of Clinical Nutrition. 2012;**95**(5):1003-1012

[87] Khaw KT, Friesen MD, Riboli E, Luben R, Wareham N. Plasma phospholipid fatty acid concentration and incident coronary heart disease in men and women: The EPIC-Norfolk prospective study. PLoS Medicine. 2012;**9**(7):e1001255

[88] Ooi EM, Ng TW, Watts GF, Barrett PH. Dietary fatty acids and lipoprotein metabolism: New insights and updates. Current Opinion in Lipidology. 2013;**24**(3):192-197

[89] McLaughlin T, Carter S, Lamendola C, et al. Effects of moderate variations in macronutrient composition on weight loss and reduction in cardiovascular disease risk in obese, insulin-resistant adults. The American Journal of Clinical Nutrition. 2006;**84**(4):813-821

[90] Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. The New England Journal of Medicine. 2003;**348**(21):2082-2090

[91] Ryan MC, Abbasi F, Lamendola C, Carter S, McLaughlin TL. Serum alanine aminotransferase levels decrease further with carbohydrate than fat restriction in insulin-resistant adults. Diabetes Care. 2007;**30**(5):1075-1080

[92] Carter P, Khunti K, Davies MJ. Dietary recommendations for the prevention of type 2 diabetes: What are they based on? Journal of Nutrition and Metabolism. 2012;**2012**:847202

[93] Kim J, Tanabe K, Yokoyama N, Zempo H, Kuno S. Association between physical activity and metabolic syndrome in middle-aged Japanese: A cross-sectional study. BMC Public Health. 2011;**11**:624

[94] Johnson NA, George J. Fitness versus fatness: Moving beyond weight loss in nonalcoholic fatty liver disease. Hepatology. 2010;**52**(1):370-381

[95] Carroll JF, Franks SF, Smith AB, Phelps DR. Visceral adipose tissue loss and insulin resistance 6 months after laparoscopic gastric banding surgery: A preliminary study. Obesity Surgery. 2009;**19**(1):47-55

[96] Rector RS, Thyfault JP, Morris RT, et al. Daily exercise increases hepatic fatty acid oxidation and prevents steatosis in Otsuka long-Evans Tokushima fatty rats. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2008;**294**(3):G619-G626

[97] Mikus CR, Rector RS, Arce-Esquivel AA, et al. Daily physical activity enhances reactivity to insulin in skeletal muscle arterioles of hyperphagic Otsuka long-Evans Tokushima fatty rats. Journal of Applied Physiology. 2010;**109**(4):1203-1210

[98] Shojaee-Moradie F, Baynes KC, Pentecost C, et al. Exercise training reduces fatty acid availability and improves the insulin sensitivity of glucose metabolism. Diabetologia. 2007;**50**(2):404-413

[99] Johnson NA, Sachinwalla T, Walton DW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology. 2009;**50**(4): 1105-1112

[100] van der Heijden GJ, Wang ZJ, Chu ZD, et al. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring). 2010;**18**(2):384-390

[101] Bonekamp S, Barone BB, Clark J, Stewart KJ. The effect of an exercise training intervention on hepatic steatosis. Hepatology. 2008;**48**(Suppl 1):806a

[102] Know your fats. American Heart Association website. http://www.heart.org/HEARTORG/Conditions/Cholesterol/PreventionTreatmentofHighCholesterol/Know-Your-Fats_UCM_305628_Article.jsp. [Accessed 06-06-2017]

[103] O'Donovan G, Kearney EM, Nevill AM, Woolf-May K, Bird SR. The effects of 24 weeks of moderate- or high-intensity exercise on insulin resistance. European Journal of Applied Physiology. 2005;**95**(5-6):522-528

[104] Kistler KD, Brunt EM, Clark JM, et al. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. The American Journal of Gastroenterology. 2011;**106**(3):460-468

[105] St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. Hepatology. 2009;**50**(1):68-76

[106] Chen SM, Liu CY, Li SR, Huang HT, Tsai CY, Jou HJ. Effects of therapeutic lifestyle program on ultrasound-diagnosed nonalcoholic fatty liver disease. Journal of the Chinese Medical Association. 2008;**71**(11):551-558

[107] de Mello MT, de Piano A, Carnier J, et al. Long-term effects of aerobic plus resistance training on the metabolic syndrome and adiponectinemia in obese adolescents. Journal of Clinical Hypertension (Greenwich, Conn.). 2011;**13**(5):343-350

[108] de Piano A, de Mello MT, Sanches LP, et al. Long-term effects of aerobic plus resistance training on the adipokines and neuropeptides in nonalcoholic fatty liver disease obese adolescents. European Journal of Gastroenterology and Hepatology. 2012;**24**(11):1313-1324

[109] Hallsworth K et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut. DOI: 10.1136/gut.2011.242073

[110] Hasegawa T, Yoneda M, et al. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with non-alcoholic steatohepatitis: A pilot study. Alimentary Pharmacology & Therapeutics. 2001;**15**:1667-1672

[111] Kugelmas M, Hill DB, Vivian B, Marsano L, CJ MC. Cytokines and NASH : A pilot study of the effects of lifestyle modification and vitamin E. Hepatology. 2003;**38**:413-419

[112] Sanyal AJ, Chalasini N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. New England Journal of Medicine. 2010;**362**:16751685. DOI: 10.1056/NEJMoa0907929

[113] Arendt BM, Allard JP. Effect of atorvastatin, vitamin E and C on nonalcoholic fatty liver disease: is the combination required? The American Journal of Gastroenterology. 2011;**106**:78-80

[114] Sesso HD, Cook NR, Buring JE, Manson JE, Gaziano JM. Alcohol consumption and the risk of hypertension in women and men. Hypertension. 2008;**51**:1080-1087. DOI: 10.1161/HYPERTENSION AHA.107.104968

[115] Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database of Systematic Reviews. 2012 Mar 14;**3**:CD007176. DOI: 10.1002/14651858.CD007176.pub2. Review

[116] Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non-diabetic adults. Diabetes Care. 2007;**30**:980-986

[117] Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the third National Health and nutrition examination survey. Atherosclerosis. 2009;**205**:255-260

[118] Musso G, Anty R, Petta S. Antioxidant therapy and drugs interfering with lipid metabolism: could they be effective in NAFLD patients? Current Pharmaceutical Design. 2013;**19**:5297-5313

[119] Di Minno MN, Russolillo A, Lupoli R, Ambrosino P, Di Minno A, et al. Omega-3 fatty acids for the treatment of non-alcoholic fatty liver disease. World Journal of Gastroenterology. 2012;**18**:5839-5847

[120] Compare D, Coccoli P, Rocco A, Nardone OM, De Maria S, Cartenì M, et al. Gut–liver axis: The impact of gut microbiota on non-alcoholic fatty liver disease. Nutrition, Metabolism & Cardiovascular Diseases. 2012;**22**:471-476. DOI: 10.1016/j.numecd.2012.02.007

[121] Loguercio C, DeSimone T, Federico A, Terracciano F, Tuccillo C, DiChicco M, Carteni M. Gut-liver axis: A new point of attack to treat chronic liver damage? The American Journal of Gastroenterology. 2002;**97**:2144-2146

[122] Loguercio C, Federico A, Tuccillo C, Terracciano F, D'Auria MV, et al. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. Journal of Clinical Gastroenterology. 2005;**39**:540-543

[123] Li X, Zhuo R, Tiong S, Di Cara F, King-Jones K, Hughes SC, Campbell SD, Wevrick R. The Smc5/Smc6/MAGE complex confers resistance to caffeine and genotoxic stress in Drosophila melanogaster. PLoS One. 2013;**8**(3):e59866

[124] Aller R, De Luis DA, Izaola O, Conde R, Gonzalez Sagrado M, Primo D, et al. Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: A double blind randomized clinical trial. European Review for Medical and Pharmacological Sciences. 2011;**15**(9):1090e5

[125] Sahebkar A. Potential efficacy of ginger as a natural supplement for nonalcoholic fatty liver disease. World Journal of Gastroenterology. 2011 Jan 14;**17**(2):271-272. DOI: 10.3748/wjg.v17.i2.271

IntechOpen