World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i28.9338

World J Gastroenterol 2014 July 28; 20(28): 9338-9344
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease

Role of diet and lifestyle changes in nonalcoholic fatty liver disease

William Nseir, Elias Hellou, Nimer Assy

William Nseir, Elias Hellou, Department of Internal Medicine, EMMS, The Nazareth Hospital, Nazareth 16100, Israel
William Nseir, Nimer Assy, Faculty of Medicine in the Galilee, Bar-Ilan University, Safed 13100, Israel
Nimer Assy, Liver Unit, Ziv Medical Center, Safed 13100, Israel
Author contributions: Nseir W wrote the manuscript and participated in the design, editing, and polishing; Hellou E participated in the design; Assy N participated in the design, editing, and polishing.
Correspondence to: William Nseir, MD, Department of Internal Medicine, EMMS, The Nazareth Hospital, POBox 11, Nazareth 16100, Israel. w.nseir@yahoo.com
Telephone: +972-4-6028851 Fax: +972-4-6028851
Received: November 4, 2013 Revised: February 24, 2014
Accepted: April 15, 2014
Published online: July 28, 2014

Abstract

Nonalcoholic fatty liver disease (NAFLD) has become one of the most common causes of liver disease worldwide and has been recognized as a major health burden. The prevalence of NAFLD has grown proportionally with the rise in obesity, sedentary lifestyle, unhealthy dietary pattern, and metabolic syndrome. Currently, there is no drug therapy that can be formulated for treating NAFLD. A combination of dietary modifications and increased physical activity remains the mainstay of NAFLD management. It is hard to maintain this mode of management; however, it seems to have significant long-term benefits. Furthermore, NAFLD patients, whether obese or not, should be educated that a healthy diet and physical activity have benefits beyond weight reduction. Further large controlled randomized trials are needed in order to identify the best dietary regimen and physical activity in the management of NAFLD patients. This review highlights the role of diet and lifestyle modifications in the management of NAFLD, and focuses on human studies regarding dietary modifications and physical activity.

Key words: Diet; Caloric restriction; Lifestyle changes; Physical activity; Aerobic exercise; Resistance exercise; Management; Nonalcoholic fatty liver disease

Core tip: To date there is no effective drug treatment for nonalcoholic fatty liver disease (NAFLD). A combination of dietary modifications and increased physical activity remains the mainstay of NAFLD therapy. In order to prevent the hepatic, extra-hepatic, including metabolic complications of NAFLD, it is important to manage this condition early. Therefore, a plan should be carried out immediately when NAFLD is diagnosed combining diet and proper exercise activity. This review highlights the role of diet and lifestyle changes in the management of NAFLD, and focuses on human studies regarding dietary modifications and physical activity.

Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver disease. *World J Gastroenterol* 2014; 20(28): 9338-9344 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i28/9338.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i28.9338

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a significant health problem worldwide. NAFLD affects 20%-30% of the adult population[1]. NAFLD can progress to nonalcoholic steatohepatitis (NASH), characterized by inflammation, apoptosis, and ballooning degeneration. This form of liver injury carries a 20%-50% risk for progressive fibrosis, 30% risk for cirrhosis, and 5% risk for hepatocellular carcinoma[2-6].

The nonstop rising incidence of obesity in today's generation is associated with many health complications

Table 1 Soft drink consumption linked with nonalcoholic fatty liver disease (mean ± SD)

Dietary constituent	NAFLD (n = 31)	Controls (n = 30)	P value
Total energy intake (kcal)	2300 ± 500	2200 ± 600	0.3
Added sugar (g/d)	75.6 ± 8.4	33.6 ± 12.6	0.001
Percent of added sugar from soft drinks	43%	8%	0.001

NAFLD: Nonalcoholic fatty liver disease.

in addition to NAFLD[7,8]. These include cardiovascular diseases, diabetes, hyperlipidemia, and hypertension. This constellation is recognized as metabolic syndrome (MetS). About 70% of patients with fatty liver have MetS and 30% of patients with MetS have fatty liver[9]. NAFLD patients have multiple components of the MetS, whether or not they are overweight or obese. Insulin resistance (IR) is present in NAFLD patients and is a significant predictor of NAFLD and NASH in most patients[10].

NAFLD is a multifactorial disease that involves a complex interaction of genetics, diet, and lifestyle, all of which combine to form the NAFLD phenotype. Currently, the only established treatment of NAFLD is the use of diet and lifestyle changes in order to decrease body weight, and to improve glycemic control, dyslipidemia, and cardiovascular risk[11-13].

As NAFLD and the other components of MetS are strongly associated with obesity, weight loss constitutes the principal key in NAFLD management. Sudden or quick weight loss achieved through dietary modification may lead to the progression of liver failure in some NAFLD patients. Alternatively, weight loss through surgical methods, even with rapid weight reduction after surgery, has been successful in reducing NAFLD progression[14-16].

This review highlights the role of diet and lifestyle modifications in the management of NAFLD, and focuses on human studies regarding dietary modifications and physical activity.

DIETARY CHANGES

Commonly, patients with NAFLD consume high caloric diets, especially in the form of carbohydrate and fats, in comparison to control population. The increased consumption of carbohydrate in the form of beverages has increased the total energy intake share from 3.9% in 1977 to 9.2% in 2001[17]. Zelber-Sagi *et al*[18] showed that NAFLD patients consume a larger quantity of soft drinks and meat than controls. Soft drinks are the leading source of added sugar worldwide and have been linked to NAFLD[19,20] (Table 1). Musso *et al*[11] noted increased protein intake among NAFLD patients. NAFLD diets in these patients also tended to have a higher content of saturated fat and cholesterol and less polyunsaturated fatty acids (PUFAs) than healthy persons (Table 2). Similar findings were observed by Cortez-Pinto *et al*[21].

Table 2 Dietary products that promote or improve nonalcoholic fatty liver disease

	Promote NAFLD	Improve NAFLD
Soft drinks	Yes	No
High fructose corn syrup	Yes	No
Processed carbohydrates	Yes	No
Saturated fatty acids	Yes	No
Polyunsaturated fatty acids	No	Yes
High protein	Yes	No
Red meat	Yes	No

NAFLD: Nonalcoholic fatty liver disease.

There is a lack of randomized clinical trials (RCTs) regarding the positive effect of foods or nutritional supplementation on NAFLD. NAFLD patients have a tendency towards a lower intake of fish rich in omega-3[18,22].

CALORIC RESTRICTION

As much as 40 years ago, Drenick *et al*[23] assigned 41 severely obese subjects to three different diet regimens of prolonged fasting, hypocaloric diet of 500 kcal/d, or intestinal bypass surgery. On repeat liver biopsy after one year, patients showed an improvement in steatosis with a mean weight loss of 40.9 kg in the prolonged fasting group and 59.5 kg in the hypocaloric diet. Similar results were obtained by Huang *et al*[24] using a diet of 1400 kcal/d among patients with NASH. Repeated liver biopsies indicated histological improvement in steatosis with a mean weight loss of 10.3 kg over a period of 6 mo. Lewis *et al*[25] investigated 18 morbidly obese subjects who underwent magnetic resonance imaging and spectroscopy (MRS) to measure liver size and fat content before and after treatment with Optifast very low caloric diet (VLCD). After six weeks, subjects had a mean weight reduction of 9 kg and 43% reduction in mean liver fat. Several studies have demonstrated that a reduction in caloric intake of 500 kcal with or without physical activity for a period of 6 mo resulted in a significant decrease in liver fat based on MRS examination[26-28]. Vitola *et al*[29] showed that moderate diet-induced weight loss decreases intrahepatic triglyceride (IHT) content and improves insulin sensitivity in the liver and skeletal muscle in obese adolescents who have normal glucose intolerance. It seems that a very low caloric diet is effective in reducing liver fat and weight. However, larger clinical randomized trials (CRT) are needed.

CARBOHYDRATE RESTRICTION

Simple carbohydrates in the diet, in particular fructose, have been linked to NAFLD[30]. As carbohydrate consumption affects glucose homeostasis and free fatty acids metabolism in the liver, carbohydrate-restricted diet also has been studied. Yancy *et al*[31] demonstrated in 120 overweight subjects with hyperlipidemia that a low-

carbohydrate, ketogenic diet (< 20 g/d), compared with low-fat, low-cholesterol, reduced-caloric diet, achieved a 12.9% weight loss and lipid profile improvement. Tendler *et al*[32] examined the effect of a low-carbohydrate diet (< 20 g/d) on hepatic steatosis in five patients with NAFLD. After 6 mo, repeated liver biopsies showed a reduction in steatosis, inflammation, and fibrosis, and a weight loss of 12.8 kg. Huang *et al*[24] placed 23 patients with biopsy-proven NASH on a diet of 45% carbohydrate, 35% fat, and 20% protein for 12 mo. They showed that in 9 of 15 patients who underwent repeated liver biopsies, there was a significant histological improvement in hepatic steatosis. Recently, a small CRT showed that short-term carbohydrate restriction is more efficacious at reducing IHT than caloric restriction[33]. In an RCT of 307 obese patients with mean BMI of 36.1 kg/m^2, both low-fat and low-carbohydrate diets decreased blood pressure, serum triglycerides, VLDL, and LDL levels[34].

FAT RESTRICTION

The composition of dietary lipid may influence the IHT. One study has demonstrated that an isocaloric high fat diet in postmenopausal women increased the IHT[35]. Furthermore, a study comparing diets of NAFLD patients with NASH patients found that patients with NASH consumed a higher percentage of calories from fat that those with steatosis alone, despite consuming fewer total calories[36]. Petersen *et al*[37] applied a 3% low-fat reduced-caloric diet (1200 kcal/d) to eight patients with NAFLD. Based on MRS they showed an 81% reduction in hepatic lipid content and weight loss of 8% over a maximum period of 16 wk.

Specific types of fat play an important role in NAFLD pathophysiology in addition to the total fat content of the diet. It is difficult to determine the effects of saturated fats independent of total calories[38]. Trans-fatty acids (TFA) are unsaturated acids with at least one double bond in the trans configuration. They are rarely found naturally in the food supply. Therefore, the role of TFA in human NAFLD needs to be studied.

Polyunsaturated fatty acids and specifically the n-3 PUFA and mono-unsaturated fatty acid may play a protective role in NAFLD (Table 2). The intake of n-3 PUFAs of marine origin leads to elevated serum concentration of adiponectin, largely independent of food intake or adiposity and decreases serum insulin, TGs, and leptin levels. These effects have been used to explain the anti-diabetic action, weight loss, and decrease in adiposity that occur with the intake of n-3 PUFA-rich diets[39-41]. In addition, PUFAs up regulate gene expression of proteins involved in fatty acid oxidation, while they decrease those involved in lipogenesis including SREBP-1[42]. n-3 PUFA concentrations are lower in patients with NAFLD, and have a higher ratio of n-6 to n-3 PUFA[43]. Capanni *et al*[22] investigated the efficacy of n-3 PUFA supplementation in 42 patients with NAFLD who were treated daily with 1 g n-3 PUFA for 12 mo in an open-label study. In addition to significantly lowering their serum AST, ALT, and GGT activities and their serum TG and fasting blood glucose levels, they found that the n-3 PUFA supplementation ameliorated the ultrasonographic and hemodynamic features of hepatic steatosis. Spadaro *et al*[44] investigated the efficacy of n-3 PUFAs in 40 patients with NAFLD, and reported that serum ALT activity, serum TG levels, as well as fatty liver improved after six mo of n-3 PUFA therapy. Eicosapentaenoic acid (EPA) is one of the most important fatty acids of the n-3 PUFAs. In a pilot trial that involved 23 patients with biopsy-proven NASH who were given 2.7 grams of EPA daily for 12 mo[45], the EPA treatment improved serum ALT and AST activities and free fatty acid levels. In six of the seven patients who agreed to have a repeat liver biopsy at the end of the study, they found an improvement in the extent of hepatic steatosis and fibrosis and the severity of the hepatic inflammation. In a preliminary study, Sofi *et al*[46] investigated the effectiveness of one-year consumption of an n-3 PUFA-rich diet in 11 patients with NAFLD. They reported that the long-term consumption of olive oil enriched with n-3 PUFAs was able to decrease serum liver enzyme activities and TG levels. In an RCT that involved 134 patients with NAFLD, Zhu *et al*[47] reported that n-3 PUFAs from seal oils are safe and efficacious in hyperlipidemic patients with NAFLD. Specifically, they found that these n-3 PUFAs can improve their serum ALT activities and serum lipid levels, and normalize hepatic fat infiltration. Oya *et al*[48] studied the association between dietary n-3 PUFAs and NAFLD in Japanese men and women, and they found that dietary EPA and EPA with DHA may be independent and preventive nutrients for NAFLD in Japanese men.

PROTEIN

The exact effect of protein on NAFLD is not so clear. Recently, it was shown that a Western dietary pattern at 14 years-of-age in a general population sample was associated with an increased risk of NAFLD at 17 years, particularly in obese adolescents[49]. Several previous studies showed a significant association between meat (red meat) consumption and NAFLD[18,50,51].

PHYSICAL ACTIVITY

Physical activity (PA) is another modality for weight reduction in NAFLD therapy. Despite the difficulties, increased PA is highly beneficial in the management of NAFLD. PA has been shown to produce a reduction of 35% for diabetes and 49% for cardiovascular diseases in patients with NAFLD[52,53]. In an observational analysis of 348 patients with NAFLD, after one year Suzuki *et al*[54] demonstrated an improvement in transaminase levels with weight loss, and they concluded that reducing weight by at least 5% with subsequent weight control and exercising regularly may be beneficial in treating NAFLD.

Sreenivasa Baba *et al*[55] reported in a pilot trial that moderate intensity in aerobic exercise helped to normalize ALT levels in 65 NASH patients receiving a moderately energy-restricted diet. Significant improvement was not noted in body mass index, serum aminotransferase levels, and fasting glucose in patients adherent to the prescribed diet and exercise regimen.

Hickman *et al*[56] followed 31 patients with NASH over a period of 3 mo with a combination of dietary modifications (55% carbohydrate, 15% protein, and 30% fat diets) and moderate exercise (150 min/wk of aerobic exercise). Patients achieved a mean weight loss of 4% with a noted significant serum alanine aminotransferase (ALT) reduction. Vilar Gomez *et al*[57], in an RCT, assigned 60 patients with liver biopsy-proven NAFLD to hypocaloric diet plus aerobic exercise daily and three Viusid sachets daily or a hypocaloric diet and exercise for a period of six mo. They showed that treatment with diet and exercise leads to a notable improvement in histological features of NAFLD.

Cross-sectional studies have shown that higher levels of PA are associated with lower levels of IHT[58-60]. Previous studies have reported a beneficial effect of aerobic exercise on liver function, independent of weight reduction[55,61]. In recent years, there has been increased attention on resistance training as a useful adjunctive tool of exercise[62,63]. Ibañez *et al*[64] showed that resistance training without a concomitant weight loss diet significantly improved insulin sensitivity and fasting glycemia and decreased abdominal fat. The benefit of PA alone in the absence of any changes in body weight was examined in NAFLD patients. Hallsworth *et al*[65] assigned 19 sedentary adults with NAFLD to 8 wk of resistance exercise (RE). Eleven were assigned to RE and eight to normal treatment; they showed a benefit of RE as a lipid-lowering treatment for NAFLD independent of weight loss. Lee *et al*[66] examined the effects of aerobic exercise versus RE without caloric restriction on abdominal adiposity, IHT, and insulin sensitivity. They concluded that both aerobic and resistance exercise alone are effective for reducing abdominal fat and IHT in obese adolescent boys. Recently, one exercise-related interventional study examined the long-term effects of aerobic and resistance training on the adipokines and neuropeptides in NAFLD obese adolescents and found a significant improvement in NAFLD biomarkers[67].

CONCLUSION

NAFLD is linked strongly to MetS and cardiovascular diseases[68], and may predict the tendency to develop diabetes. The most common cause of death in patients with NAFLD is cardiovascular disease, not chronic liver disease[69,70]. Therefore, to detect and manage NAFLD early is the mainstay in preventing hepatic, extra-hepatic, and metabolic complications. Nutrition has been demonstrated to be associated with NAFLD and NASH[18-21,35]. Currently, no firm recommendations can be formulated for treating NAFLD or NASH due to lack of high quality, large CRT, and strong evidence-based data with hepatic histopathological evidence. Based on available data, patients with NAFLD should optimally achieve a 5%-10% weight reduction (avoid rapid weight loss of more than 1.6 kg/wk). NAFLD patients, whether obese or of normal weight, should be informed that a healthy diet has benefits beyond weight reduction. They should be advised to reduce saturated/trans-fat and to increase polyunsaturated fat with special emphasis on omega-3 fatty acids (1 g/d fish oil), reduce added sugar to its minimum, and avoid soft drinks containing sugar (including fruit juices that contain a lot of fructose). For those who are red meat eaters, less meat and increased fish consumption, increased fiber intake, and minimizing fast food intake should be recommended.

Physical activity as aerobic or resistance exercise or combination should be integrated strongly in NAFLD management. Nutritional counseling with a multidisciplinary team including dietitians, psychologists, and physical activity supervisors is the preferable method in the management of NAFLD patients.

REFERENCES

1 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395 [PMID: 15565570 DOI: 10.1002/hep.20466]

2 **Matteoni CA**, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413-1419 [PMID: 10348825]

3 **Willner IR**, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. *Am J Gastroenterol* 2001; **96**: 2957-2961 [PMID: 11693332 DOI: 10.1111/j.1572-0241.2001.04667.x]

4 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMra011775]

5 **Bugianesi E**, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P, Capussotti L, Salizzoni M, Rizzetto M. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; **123**: 134-140 [PMID: 12105842]

6 **Starley BQ**, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010; **51**: 1820-1832 [PMID: 20432259 DOI: 10.1002/hep.23594]

7 **Pi-Sunyer FX**. The obesity epidemic: pathophysiology and consequences of obesity. *Obes Res* 2002; **10** Suppl 2: 97S-104S [PMID: 12490658 DOI: 10.1038/oby.2002.202]

8 **Haynes P**, Liangpunsakul S, Chalasani N. Nonalcoholic fatty liver disease in individuals with severe obesity. *Clin Liver Dis* 2004; **8**: 535-47, viii [PMID: 15331062 DOI: 10.1016/j.cld.2004.04.007]

9 **Alberti KG**, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart

Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640-1645 [PMID: 19805654 DOI: 10.1161/CIRCULATIONAHA.109.192644]
10 **Clark JM**. The epidemiology of nonalcoholic fatty liver disease in adults. *J Clin Gastroenterol* 2006; **40** Suppl 1: S5-10 [PMID: 16540768 DOI: 10.1097/01.mcg.0000168638.84840.ff]
11 **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* 2003; **37**: 909-916 [PMID: 12668986 DOI: 10.1053/jhep.2003.50132]
12 **Clark JM**. Weight loss as a treatment for nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2006; **40** Suppl 1: S39-S43 [PMID: 16540766 DOI: 10.1097/01.mcg.0000168641.31321.fa]
13 **Hollingsworth KG**, Abubacker MZ, Joubert I, Allison ME, Lomas DJ. Low-carbohydrate diet induced reduction of hepatic lipid content observed with a rapid non-invasive MRI technique. *Br J Radiol* 2006; **79**: 712-715 [PMID: 16940371]
14 **Weiner RA**. Surgical treatment of non-alcoholic steatohepatitis and non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 274-279 [PMID: 20460923 DOI: 10.1159/000282102]
15 **Mathurin P**, Hollebecque A, Arnalsteen L, Buob D, Leteurtre E, Caiazzo R, Pigeyre M, Verkindt H, Dharancy S, Louvet A, Romon M, Pattou F. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. *Gastroenterology* 2009; **137**: 532-540 [PMID: 19409898 DOI: 10.1053/j.gastro.2009.04.052]
16 **Furuya CK**, de Oliveira CP, de Mello ES, Faintuch J, Raskovski A, Matsuda M, Vezozzo DC, Halpern A, Garrido AB, Alves VA, Carrilho FJ. Effects of bariatric surgery on nonalcoholic fatty liver disease: preliminary findings after 2 years. *J Gastroenterol Hepatol* 2007; **22**: 510-514 [PMID: 17376042]
17 **Nielsen SJ**, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med* 2004; **27**: 205-210 [PMID: 15450632 DOI: 10.1016/j.amepre.2004.05.005]
18 **Zelber-Sagi S**, Nitzan-Kaluski D, Goldsmith R, Webb M, Blendis L, Halpern Z, Oren R. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. *J Hepatol* 2007; **47**: 711-717 [PMID: 17850914]
19 **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. *J Hepatol* 2009; **51**: 918-924 [PMID: 19765850 DOI: 10.1016/j.jhep.2009.05.033]
20 **Assy N**, Nasser G, Kamayse I, Nseir W, Beniashvili Z, Djibre A, Grosovski M. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. *Can J Gastroenterol* 2008; **22**: 811-816 [PMID: 18925303]
21 **Cortez-Pinto H**, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME. How different is the dietary pattern in non-alcoholic steatohepatitis patients? *Clin Nutr* 2006; **25**: 816-823 [PMID: 16677739 DOI: 10.1016/j.clnu.2006.01.027]
22 **Capanni M**, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, Svegliati-Baroni G, Sofi F, Milani S, Abbate R, Surrenti C, Casini A. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. *Aliment Pharmacol Ther* 2006; **23**: 1143-1151 [PMID: 16611275 DOI: 10.1111/j.1365-2036.2006.02885.x]
23 **Drenick EJ**, Simmons F, Murphy JF. Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass. *N Engl J Med* 1970; **282**: 829-834 [PMID: 5418545 DOI: 10.1056/NEJM197004092821502]
24 **Huang MA**, Greenson JK, Chao C, Anderson L, Peterman D, Jacobson J, Emick D, Lok AS, Conjeevaram HS. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. *Am J Gastroenterol* 2005; **100**: 1072-1081 [PMID: 15842581]
25 **Lewis MC**, Phillips ML, Slavotinek JP, Kow L, Thompson CH, Toouli J. Change in liver size and fat content after treatment with Optifast very low calorie diet. *Obes Surg* 2006; **16**: 697-701 [PMID: 16756727 DOI: 10.1381/096089206777346682]
26 **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**: 2162-2168 [PMID: 19390517 DOI: 10.1038/oby.2009.126]
27 **Larson-Meyer DE**, Newcomer BR, Heilbronn LK, Volaufova J, Smith SR, Alfonso AJ, Lefevre M, Rood JC, Williamson DA, Ravussin E. Effect of 6-month calorie restriction and exercise on serum and liver lipids and markers of liver function. *Obesity* (Silver Spring) 2008; **16**: 1355-1362 [PMID: 18421281 DOI: 10.1038/oby.2008.201]
28 **Thomas EL**, Brynes AE, Hamilton G, Patel N, Spong A, Goldin RD, Frost G, Bell JD, Taylor-Robinson SD. Effect of nutritional counselling on hepatic, muscle and adipose tissue fat content and distribution in non-alcoholic fatty liver disease. *World J Gastroenterol* 2006; **12**: 5813-5819 [PMID: 17007047]
29 **Vitola BE**, Deivanayagam S, Stein RI, Mohammed BS, Magkos F, Kirk EP, Klein S. Weight loss reduces liver fat and improves hepatic and skeletal muscle insulin sensitivity in obese adolescents. *Obesity* (Silver Spring) 2009; **17**: 1744-1748 [PMID: 19498349 DOI: 10.1038/oby.2009.171]
30 **Nseir W**, Nassar F, Assy N. Soft drinks consumption and nonalcoholic fatty liver disease. *World J Gastroenterol* 2010; **16**: 2579-2588 [PMID: 20518077]
31 **Yancy WS**, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med* 2004; **140**: 769-777 [PMID: 15148063]
32 **Tendler D**, Lin S, Yancy WS, Mavropoulos J, Sylvestre P, Rockey DC, Westman EC. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2007; **52**: 589-593 [PMID: 17219068 DOI: 10.1007/s10620-006-9433-5]
33 **Browning JD**, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr* 2011; **93**: 1048-1052 [PMID: 21367948 DOI: 10.3945/ajcn.110.007674]
34 **Foster GD**, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, Stein RI, Mohammed BS, Miller B, Rader DJ, Zemel B, Wadden TA, Tenhave T, Newcomb CW, Klein S. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010; **153**: 147-157 [PMID: 20679559 DOI: 10.7326/0003-4819-153-3-201008030-00005]
35 **Westerbacka J**, Lammi K, Häkkinen AM, Rissanen A, Salminen I, Aro A, Yki-Järvinen H. Dietary fat content modifies liver fat in overweight nondiabetic subjects. *J Clin Endocrinol Metab* 2005; **90**: 2804-2809 [PMID: 15741262 DOI: 10.1210/jc.2004-1983]
36 **Vilar L**, Oliveira CP, Faintuch J, Mello ES, Nogueira MA, Santos TE, Alves VA, Carrilho FJ. High-fat diet: a trigger of non-alcoholic steatohepatitis? Preliminary findings in obese subjects. *Nutrition* 2008; **24**: 1097-1102 [PMID: 18640006 DOI: 10.1016/j.nut.2008.05.017]
37 **Petersen KF**, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; **54**: 603-608 [PMID: 15734833]
38 **Brøns C**, Jensen CB, Storgaard H, Hiscock NJ, White A, Appel JS, Jacobsen S, Nilsson E, Larsen CM, Astrup A, Quistorff B, Vaag A. Impact of short-term high-fat feeding on glucose and insulin metabolism in young healthy men. *J Physiol* 2009; **587**: 2387-2397 [PMID: 19332493 DOI: 10.1113/

jphysiol.2009.169078]
39 **Yu S**, Rao S, Reddy JK. Peroxisome proliferator-activated receptors, fatty acid oxidation, steatohepatitis and hepatocarcinogenesis. *Curr Mol Med* 2003; **3**: 561-572 [PMID: 14527087]
40 **Flachs P**, Mohamed-Ali V, Horakova O, Rossmeisl M, Hosseinzadeh-Attar MJ, Hensler M, Ruzickova J, Kopecky J. Polyunsaturated fatty acids of marine origin induce adiponectin in mice fed a high-fat diet. *Diabetologia* 2006; **49**: 394-397 [PMID: 16397791 DOI: 10.1007/s00125-005-0053-y]
41 **Nseir W**, Mograbi J, Ghali M. Lipid-lowering agents in nonalcoholic fatty liver disease and steatohepatitis: human studies. *Dig Dis Sci* 2012; **57**: 1773-1781 [PMID: 22419057 DOI: 10.1007/s10620-012-2118-3]
42 **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]
43 **Araya J**, Rodrigo R, Videla LA, Thielemann L, Orellana M, Pettinelli P, Poniachik J. Increase in long-chain polyunsaturated fatty acid n - 6/n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. *Clin Sci* (Lond) 2004; **106**: 635-643 [PMID: 14720121 DOI: 10.1042/CS20030326]
44 **Spadaro L**, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, Papa G, Rabuazzo AM, Purrello F. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Dig Liver Dis* 2008; **40**: 194-199 [PMID: 18054848 DOI: 10.1016/j.dld.2007.10.003]
45 **Tanaka N**, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2008; **42**: 413-418 [PMID: 18277895 DOI: 10.1097/MCG.0b013e31815591aa]
46 **Sofi F**, Giangrandi I, Cesari F, Corsani I, Abbate R, Gensini GF, Casini A. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. *Int J Food Sci Nutr* 2010; **61**: 792-802 [PMID: 20465434 DOI: 10.3109/09637486.2010.487480]
47 **Zhu FS**, Liu S, Chen XM, Huang ZG, Zhang DW. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. *World J Gastroenterol* 2008; **14**: 6395-6400 [PMID: 19009658]
48 **Oya J**, Nakagami T, Sasaki S, Jimba S, Murakami K, Kasahara T, Wasada T, Sekiguchi H, Hasegawa M, Endo Y, Iwamoto Y. Intake of n-3 polyunsaturated fatty acids and non-alcoholic fatty liver disease: a cross-sectional study in Japanese men and women. *Eur J Clin Nutr* 2010; **64**: 1179-1185 [PMID: 20683463 DOI: 10.1038/ejcn.2010.139]
49 **Oddy WH**, Herbison CE, Jacoby P, Ambrosini GL, O'Sullivan TA, Ayonrinde OT, Olynyk JK, Black LJ, Beilin LJ, Mori TA, Hands BP, Adams LA. The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. *Am J Gastroenterol* 2013; **108**: 778-785 [PMID: 23545714 DOI: 10.1038/ajg.2013.95]
50 **Shi L**, Liu ZW, Li Y, Gong C, Zhang H, Song LJ, Huang CY, Li M. The prevalence of nonalcoholic fatty liver disease and its association with lifestyle/dietary habits among university faculty and staff in Chengdu. *Biomed Environ Sci* 2012; **25**: 383-391 [PMID: 23026517 DOI: 10.3967/0895-3988.2012.04.002]
51 **Kim CH**, Kallman JB, Bai C, Pawloski L, Gewa C, Arsalla A, Sabatella ME, Younossi ZM. Nutritional assessments of patients with non-alcoholic fatty liver disease. *Obes Surg* 2010; **20**: 154-160 [PMID: 18560947 DOI: 10.1007/s11695-008-9549-0]
52 **Bassuk SS**, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. *J Appl Physiol* (1985) 2005; **99**: 1193-1204 [PMID: 16103522 DOI: 10.1152/japplphysiol.00160.2005]
53 **LaMonte MJ**, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol* (1985) 2005; **99**: 1205-1213 [PMID: 16103523 DOI: 10.1152/japplphysiol.00193.2005]
54 **Suzuki A**, Lindor K, St Saver J, Lymp J, Mendes F, Muto A, Okada T, Angulo P. Effect of changes on body weight and lifestyle in nonalcoholic fatty liver disease. *J Hepatol* 2005; **43**: 1060-1066 [PMID: 16140415 DOI: 10.1016/j.jhep.2005.06.008]
55 **Sreenivasa Baba C**, Alexander G, Kalyani B, Pandey R, Rastogi S, Pandey A, Choudhuri G. Effect of exercise and dietary modification on serum aminotransferase levels in patients with nonalcoholic steatohepatitis. *J Gastroenterol Hepatol* 2006; **21**: 191-198 [PMID: 16706832 DOI: 10.1111/j.1440-1746.2005.04233.x]
56 **Hickman IJ**, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, Powell EE. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* 2004; **53**: 413-419 [PMID: 14960526]
57 **Vilar Gomez E**, Rodriguez De Miranda A, Gra Oramas B, Arus Soler E, Llanio Navarro R, Calzadilla Bertot L, Yasells Garcia A, Del Rosario Abreu Vazquez M. Clinical trial: a nutritional supplement Viusid, in combination with diet and exercise, in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2009; **30**: 999-1009 [PMID: 19691668 DOI: 10.1111/j.1365-2036.2009.04122.x]
58 **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**: 68-76 [PMID: 19444870 DOI: 10.1002/hep.22940]
59 **Perseghin G**, Lattuada G, De Cobelli F, Ragogna F, Ntali G, Esposito A, Belloni E, Canu T, Terruzzi I, Scifo P, Del Maschio A, Luzi L. Habitual physical activity is associated with intrahepatic fat content in humans. *Diabetes Care* 2007; **30**: 683-688 [PMID: 17327341 DOI: 10.2337/dc06-2032]
60 **Zelber-Sagi S**, Nitzan-Kaluski D, Goldsmith R, Webb M, Zvibel I, Goldiner I, Blendis L, Halpern Z, Oren R. Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. *Hepatology* 2008; **48**: 1791-1798 [PMID: 18972405 DOI: 10.1002/hep.22525]
61 **Johnson NA**, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, George J. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology* 2009; **50**: 1105-1112 [PMID: 19637289 DOI: 10.1002/hep.23129]
62 **Albright A**, Franz M, Hornsby G, Kriska A, Marrero D, Ullrich I, Verity LS. American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Med Sci Sports Exerc* 2000; **32**: 1345-1360 [PMID: 10912903]
63 **Pollock ML**, Franklin BA, Balady GJ, Chaitman BL, Fleg JL, Fletcher B, Limacher M, Piña IL, Stein RA, Williams M, Bazzarre T. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* 2000; **101**: 828-833 [PMID: 10683360]
64 **Ibañez J**, Izquierdo M, Argüelles I, Forga L, Larrión JL, García-Unciti M, Idoate F, Gorostiaga EM. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. *Diabetes Care* 2005; **28**: 662-667 [PMID: 15735205]
65 **Hallsworth K**, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, Day CP, Trenell MI. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut* 2011; **60**: 1278-1283 [PMID: 21708823 DOI: 10.1136/gut.2011.242073]

66 **Lee S**, Bacha F, Hannon T, Kuk JL, Boesch C, Arslanian S. Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. *Diabetes* 2012; **61**: 2787-2795 [PMID: 22751691 DOI: 10.2337/db12-0214]

67 **de Piano A**, de Mello MT, Sanches Pde L, da Silva PL, Campos RM, Carnier J, Corgosinho F, Foschini D, Masquio DL, Tock L, Oyama LM, do Nascimento CM, Tufik S, Dâmaso AR. Long-term effects of aerobic plus resistance training on the adipokines and neuropeptides in nonalcoholic fatty liver disease obese adolescents. *Eur J Gastroenterol Hepatol* 2012; **24**: 1313-1324 [PMID: 22932160 DOI: 10.1097/MEG.0b013e32835793ac]

68 **Nseir W**, Shalata A, Marmor A, Assy N. Mechanisms linking nonalcoholic fatty liver disease with coronary artery disease. *Dig Dis Sci* 2011; **56**: 3439-3449 [PMID: 21655948 DOI: 10.1007/s10620-011-1767-y]

69 **Söderberg C**, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology* 2010; **51**: 595-602 [PMID: 20014114 DOI: 10.1002/hep.23314]

70 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/hep.21327]

P- Reviewer: Charatcharoenwitthaya P, Miura K
S- Editor: Zhai HH **L- Editor**: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com