ADVANCES IN FOOD TECHNOLOGY AND NUTRITIONAL SCIENCES

Openventio PUBLISHERS

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

Literature Review

Corresponding author
Mehdi Foroughi, MSc
Department of Nutrition Sciences
College of Nutrition Sciences
Isfahan University of Medical Sciences
Isfahan, Iran
Tel. +989134136774
E-mail: Mforoughi38@yahoo.com

Volume 2 : Issue 2
Article Ref. #: 1000AFTNSOJ2130

Article History
Received: June 28th, 2016
Accepted: August 2nd, 2016
Published: August 3rd, 2016

Citation
Jafari S, Hajinasrollah E, Foroughi M. Non-alcoholic fatty liver disease and nutrition: A literature review. *Adv Food Technol Nutr Sci Open J*. 2016; 2(2): 51-63. doi: 10.17140/AFTNSOJ-2-130

Non-Alcoholic Fatty Liver Disease and Nutrition: A Literature Review

Sahar Jafari, MSc[1]; Esmail Hajinasrollah, MD[2]; Mehdi Foroughi, MSc[3*]

[1]Department of Nutrition Sciences, College of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[2]Loghman Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Nutrition Science, College of Nutrition Sciences, Isfahan University of Medical Science, Isfahan, Iran

KEYWORDS: Non-Alcoholic Fatty Liver; Obesity; Patients; Weight loss.

ABBREVIATIONS: NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: Body Mass Index; TG: Triglyceride; VLDL: Very Low Density Lipoprotein; PUFA: Polyunsaturated fatty acid; MUFA: Monounsaturated fatty acids; FFQ: Food Frequency Questionnaire; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; MCD: Methionine and choline deficient; AGEs: Advanced glycation end products; MRI: Magnetic Resonance Imaging; CDC: Centers of Prevention and Control of Diseases.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is considered as a well-known disease which is determined by without using alcohol. There is high prevalence of non-alcoholic fatty liver in the community and this condition potentially can progress to hepatic cirrhosis and hepatic defect.[1-3] In developed country, it is estimated that 20% to 30% of adult populations have non-alcoholic fatty liver.[4-8] 50% of diabetic people and approximately 80% of obese people with morbidity obesity are having non-alcoholic fatty liver.[6,9-10] Prevalence of non-alcoholic fatty liver in Western countries is likely concurrent with epidemic obesity and also it is associated with metabolic disorders.[5,11-14] Patients with non-alcoholic fatty liver usually have insulin resistance.[14-19] The prevalence of non-alcoholic fatty liver has been increased in individuals who have normal body mass index (BMI). However, these people have central obesity and latent insulin resistance.[17,18,20,21] In epidemiologic studies, these patients with normal weight have unhealthy diet.[22-24]

The efficacy and immunity of medication therapy is unclear towards treatment of non-alcoholic fatty liver.[25] Obesity has the most correlation with non-alcoholic fatty liver.[26] Therefore, to modify the lifestyle is the first line treatment for non-alcoholic fatty liver. Managing the non-alcoholic fatty liver includes gradually decreasing the weight and increasing the physical activity.[27-33]

Studies did not determine which material or micronutrient in the diet potentially increases the risk of developing to non-alcoholic fatty liver; however, it is obvious that keeping low weight will be difficult in long term.[34] To change the diet composition without decreasing the rate of calorie will be a practical and realistic variation for treatment of non-alcoholic fatty liver. Therefore, it is very important to evaluate the relationship between particular micronutrients and compounds of diet to non-alcoholic fatty liver.

This review study has been performed on epidemiological studies which evaluated the relationship between non-alcoholic fatty liver to diet compounds, weight loss, and physical activity.

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

CARBOHYDRATE AND FAT CONTENT OF DIET

Three main sources are available for increasing the triglyceride (TG) concentration in liver. These sources include increased inflow of free fatty acids from internal tissues to liver, increased intra-hepatic lipogenesis and increased receiving of fatty diet. The recent human studies suggested that high amount of fat in diet is removed by liver.[35,36] Therefore, post-prandial high changes in the rate of fat metabolism may be observed in patients with non-alcoholic fatty liver. In a study consisting of 15 patients with non-alcoholic fatty liver and 15 healthy people, the total rate of TG and very low density lipoprotein (VLDL) was higher in individuals with non-alcoholic fatty liver after receiving the single oral fat. The rate of ApoB48 and ApoB100 did not change after receiving fat by patients with non-alcoholic fatty liver. These findings suggested that increased removing of TG in the post-prandial period was associated with decreased secretion of VLDL which in turn increases the rate of hepatic steatosis.[37] The relationship between total fat of diet and the content of liver fat has been studied directly in the human studies. In a cross-sectional study, 10 obese women received two types of diets with equal rate of calories during two weeks. The rate of fat in one diet was 16% and 56% in the other one. The rate of fatty liver was measured by spectrophotometer. The rate of liver content was decreased up to 20% by using ow fat diet, however, it is increased up to 35% by using high fat diet. The rate of changes in fatty liver was concurrent to changes in the rate of fasting plasma insulin. These changes are considered very important because people did not change their weight during the study.[36] In the other study, the bariatric surgery was performed on 74 patients with morbidity obesity (90% developed to non-alcoholic fatty liver). The diet of these patients was evaluated through a 24-hour recall. The rate of consuming the meals was compared to liver histological data. There was not any meaningful correlation between the rates of received calorie or proteins to steatosis, fibrosis and hepatitis. Nevertheless, taking the high carbohydrate (approximately 56%) had significantly correlation to the rate of inflammation. However, the rate of taking the fat had reverse correlation to the rate of inflammation.[38-40] The findings of this study determine neither the correlation between each kind of dietary fats to non-alcoholic fatty liver nor the correlation between each kind of simple or complex carbohydrate to the rate of inflammation and histological findings in the patients with non-alcoholic fatty liver.[41] The correlation between carbohydrate and non-alcoholic fatty liver was evaluated in one study. The diet of 28 patients with non-alcoholic steatohepatitis was compared to 18 patients with simple steatosis. This study determined that receiving carbohydrate in group with non-alcoholic steatohepatitis was much more than the other group. Especially, the rate of taking simple carbohydrate was higher in the group with non-alcoholic steatohepatitis.

It is reasonable that fat and carbohydrate should be consumed according to recommendable rates (according to the recommendations of the American Heart Institute). Therefore, it is emphasized that the components of fat and the kind of carbohydrates (simple and complex) should be changed in the diet of patients with non-alcoholic fatty liver.

Types of Fat in Diet and Other Micronutrients

Contrary to metabolic and cardiovascular diseases, there are sparse epidemiologic studies that evaluate the correlation between the types of fat in diet to the rate of fatty liver.[5] One study was performed with low number of samples but the diet was evaluated accurately (based on 7 days of recording the food intake). 25 patients with non-alcoholic steatohepatitis were compared to the control group in terms of their diets. The diet of patients with non-alcoholic fatty liver was rich of saturated fat and cholesterol, but the content of polyunsaturated fatty acid (PUFA), fiber, ascorbic acid and tocopherol were very low in their diet.[37] The results of this study were supported by the other study and ratio of the receiving the unsaturated fatty acid to saturated fatty acid in the both groups of non-alcoholic steatohepatitis and fatty liver were lower than control group.[42] The relationship between the kind of fat in the diet to the oxidative stress markers was evaluated in patients with non-alcoholic fatty liver.[43,44] Diet analysis has been done by using of a Food frequency Questionnaire in 43 people with non-alcoholic steatohepatitis and 33 healthy people. There was negative relationship between saturated fat and total received fat to the ratio of glutathione with oxidized glutathione of plasma to fiber, carbohydrate, monounsaturated fatty acids (MUFA) and PUFA.[45,46]

Several kinds of fats can have protective effect on non-alcoholic fatty liver. It is proved that omega 3 improves non-alcoholic fatty liver. The lab studies demonstrated that the diet rich of omega 3 increased the insulin sensitivity in rats.[44] In addition, it decreases the rate of intra hepatic TG and also it improves steatohepatitis.[45,46]

Two observational studies determined that the rate of omega 3 consumption is low in patients with non-alcoholic fatty liver. In the first study which was performed as case-control study, 45 patients with non-alcoholic fatty liver were adjusted to 856 people in control group in the terms of age and sex.[45] The history of diet was evaluated through food frequency questionnaire (FFQ). The results of study demonstrated that intake of omega 6 and the ratio of omega 6 to omega 3 was higher in the patients with non-alcoholic fatty liver. These results suggested that the quality and quantity of the received fat is more likely higher than the rate of calorie in patients with non-alcoholic fatty liver.

The second cross-sectional study was performed on 349 volunteers. The history of diet was assessed by FFQ. The results of the study indicated that the patients with non-alcoholic fatty liver consumed more red meat and less fish (rich of omega 3). The red meat is rich in omega 6 in terms of fatty acid. Therefore, data suggested that consuming higher red meat increases the ratio of omega 6 to omega 3 in patients with non-alcoholic fatty liver.[47] Two clinical trials suggested the protective role of omega 3 in patients with non-alcoholic fatty liver. The first study was a non randomized controlled study which evaluated the ef-

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

fect of receiving one year complementary dose of 1000 mg/day omega 3 (EPA, DHA) by 42 patients with non-alcoholic fatty liver compared to 14 people as control group. PUFA supplement significantly improved the serum enzymes (alanine aminotransaminase (ALT), aspartate transaminase (AST), and Gamma Glutamyl Transferase (GGT)) and it decreased the rate of fat development in liver.[48] The second non-control clinical trial was performed on 23 patients with non-alcoholic fatty liver. These patients received 2700 mg EPA/per day for one year. The level of serum ALT has been improved meaningfully. 7 subjects were under hepatic biopsy after treatment. The sampling demonstrated that the rate of inflammation, steatosis and fibrosis has been improved.[49] In the both clinical trials, the body weight did not change.

There are sparse studies about the relationship between trans-fatty acids and MUFA to non-alcoholic fatty liver. So, further investigations should be performed on fatty liver and trans-fatty acids as well as MUFA.

Trans-Fatty Acids

Quantitative studies were performed to determine the role of trans-fatty acids in the development of non-alcoholic fatty liver. Consuming trans-fatty acids increases the risk of developing insulin resistance and cardiovascular diseases.[50,51]

In a study which was performed on Syria rats, one group was given PUFA and the other group was given trans-fatty acids. A group who received trans-fatty acids developed impaired glucose tolerance. In addition, the rate of insulin resistance had increased in this rats.[52] In one study, the effect of Western lifestyle was tested on Syria rats. The rate of liver steatosis significantly increased in rats which received trans-fatty acids associated with beverages rich of fructose.[53] Therefore, the role of trans-fatty acids should be evaluated in progress of the non-alcoholic fatty liver.

MUFA

Oleic acid is consumed as the main source of MUFA in the diet. Olive oil is the most important source of oleic acid (other sources are avocado and seeds). MUFA decreases the blood lipid indices, and it reduces the ratio of low-density lipoprotein (LDL) and total cholesterol to high-density lipoprotein (HDL) as well. In one meta-analysis study, the effect of various diets on lipid and glycemic indices has been evaluated. The result of this meta-analysis indicated that diets rich of monounsaturated fatty acids decreases TG concentration and blood cholesterol 19% and 22%, respectively. Also, it increases the rate of HDL but it does not affect LDL.[54,55]

In one study, rats received methionine and choline deficient (MCD) diet (lack of colin and methionine) associated with monounsaturated fatty acids. Olive oil decreased the rate of TG concentration in liver up to 30% compared to the other rats that received only MCD diet. Olive oil improves the rate of insulin resistance, increases the rate of hepatic secretion of TG, and decreases the TG flow from the peripheral organs to liver.[56] The rate of hepatosteatosis was improved in the rats that received olive oil associated with balanced diet.[57] Contrary to polyunsaturated oil, olive oil prevents progression of hepatic fibrosis.[58] Nevertheless, it is unclear whether the patients with non-alcoholic fatty liver have received olive oil or MUFA less than healthy people. The role of MUFA in development or improvement of non-alcoholic fatty liver is not fully understood.

CHOLESTEROL

The observational studies for cholesterol indicated controversial results. Some studies concluded that there is not any difference between the rate of intake cholesterol in patients with non-alcoholic fatty liver and control group.[47-59] Nevertheless, Musso et al[18] in a study showed that people with non-alcoholic fatty liver intake higher cholesterol. Also, a recent study advocated the role of cholesterol of diet in the development of non-alcoholic fatty liver. In this study, 12 subjects with normal weight who developed to non-alcoholic fatty liver were compared to 44 obese subjects with non-alcoholic fatty liver. It should be considered that the rate of intake cholesterol in first group was very higher than second group; however, the rate of intake of unsaturated fatty acids was very low in first group. Therefore, this difference in consuming cholesterol and PUFA likely is associated with progress of non-alcoholic fatty liver in people with normal weight.[24] In one study on the non-obese animal models, it was shown that diet rich of cholesterol causes non-alcoholic fatty liver.[60] Increased cholesterol in diet results in increasing the synthesis of fatty acids in hepatic cells.[24] Eventually, further investigations are required to determine the effect of various diets with different fats and the effect of these fats on progression or improvement of non-alcoholic fatty liver.

The Relationship between Sweetened Beverages and Non-alcoholic Fatty Liver

The sweetened beverages have increased the sugar consumption throughout the world.[61] In the recent decades, consumption of sweetened beverages has elevated in the world.[62] The recent studies (2005-2006) demonstrated that children and adults intake 172 and 175 Kcal/day, respectively due to drinking sweetened beverages.[63] Consumption of sweetened beverages is associated with the risk of developing obesity, diabetes, metabolic syndrome, fatty liver, and related cardiac diseases which result from increased intake of calorie as well as very rapid absorption of the available sugar in these beverages.[59,64-69]

The diets rich of sucrose increase the TG synthesis in the liver. It is evident that the rats and human who intake diet rich of fructose and sucrose are developed to fatty liver.[70] Therefore, it is reasonable that patients with non-alcoholic fatty liver should lower fructose intake.[71] In addition, the sweetened beverages such as cola have caramel dye and they are rich of advanced glycation end products (AGEs). These compounds increase the insulin and inflammation resistance.[61] In the recent years, some

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

studies confirmed the relationship between non-alcoholic fatty liver and consumption of sweetened beverages.[22,59,72,73] In a study, 31 people with normal weight that developed to non-alcoholic fatty liver were compared to 30 healthy subjects. The patients with non-alcoholic fatty liver significantly consumed sweetened beverages (43% more) and juices (8% more).[22] In the other study, patients with non-alcoholic fatty liver were compared to control group. The patients with fatty liver received sweetened beverages twofold than control group.[72]

In one study after adjusting for age, sex and calorie intake on 427 participants with non-alcoholic fatty liver disease, it was demonstrated that daily fructose intake meaningfully was associated with hepatic fibrosis directly.[74]

Generally, it should be considered that sweetened beverages play a significant role in developing to non-alcoholic fatty liver. The physician should ask the patient questions about the history of drinking sweetened beverages.

THE PATTERN OF WESTERN DIET AND FAST FOOD

Meals have different kind of food materials and the compound of food materials can have synergistic effect on each other or they can interfere.[75] The investigators consider Western diet as diet with higher fructose, sweetened beverages,[22,59,72] red meat,[47,59] cholesterol, saturated fatty acids,[47-59] lower fiber,[47] vegetables and fruits.[23] This diet has direct correlation to development of non-alcoholic fatty liver.

In human, fast food consumption has a direct correlation to increased insulin resistance. In coronary artery risk development in young adults (CARDIA) study, the results of the prospective study during 15 years on 3031 participants with non-alcoholic fatty liver demonstrated that people who eat more fast food (more than 2 times in week) are overweight (>4.5 kg) and have insulin resistance twofold than people who eat fast food less than once a week.[76] In an animal trial, a diet similar to fast food results in impaired hepatic cells.[53] In one study on 18 healthy students, they had received fast food 2 times a day for 4 weeks. The rate of taking energy and weight of these people increased and the rate of insulin resistance became twofold. Also, the rate of serum TG and ALT increased in this people.[77] These foods are rich of energy, saturated fatty acids and trans-fatty acids, simple carbohydrates, and fructose, but they have little fiber. As a result, they increase the fatty acids in liver and they produce local inflammation.[78]

WEIGHT LOSS

In the past decades, during the clinical trials three types of diet have been prescribed for reducing the weight of the patient with non-alcoholic fatty liver. The first diet is very low calorie diet (VLCD) that significantly decreases the weight. The second diet in clinical trials is the balanced diet associated with physical activity and behavior therapy. The third diet is associated with the lifestyle modification.

The examples from first diet includes the number of clinical trials in decades of 1970 and 1960,[79,80] a low calorie diet (1500 Kcal) and/or fasting that has significantly decreased weight. Steatosis had been decreased in all patients, however, it damaged liver, increased the hepatic necrosis and fibrosis in people with abruptly decreased weight.

In one study which was performed by Anderson et al[81] in 1991, 41 subjects with mortality obesity received a diet associated with a formula generating 400 Kcal. The rate of steatosis was improved but it increased 24% inflammation in hepatic duct and increased hepatic fibrosis. In the other study, VLCD diet with more low weight or equal to 10% normalized hepatic enzymes.[82] Two studies with small sample evaluated the effect of a standard diet associated with gradual decreasing of weight on histology of liver.[83] In a study, after three months treatment there was significantly improvement in the rate of steatosis as well as hepatic inflammation and fibrosis.

In a study on 15 participants with fatty liver, these persons received a standard diet along with behavior therapy. The weight of 9 subjects among 15 reduced up to 7% and as a result it improved the condition non-alcoholic fatty liver; however, in 6 subjects the weight and also of fat concentration in liver did not change.[84]

In the other study, 32 patients with non-alcoholic fatty liver divided to two groups randomly. One group only received education about lifestyle modification (control group) and the other group received a weight loss diet and physical activity (case group).[85] The rate of steatosis in the case group significantly improved than control group. The participants with more than 7% weight loss demonstrated meaningfully improvement in the rate of steatosis and hepatic duct inflammation.

In a clinical trial, Erlistat was used for decreasing the weight in patients with non-alcoholic fatty liver, and 9% weight loss improved steatosis in these patients.[86] In the other study, the lifestyle of participants with non-alcoholic fatty liver and diabetes type II were modified. These patients were given a weight loss diet associated with increased physical activity for 12 months. The control group received some recommendations about improved nutrition and physical activity. After 12 months the case group had more weight loss (approximately 8.5%) than control group and the rate of hepatic steatosis was improved.[87]

In a clinical trial by Suzuki et al,[88] 348 participants with increased ALT received an instructional brochure for weight loss diet. After three months, these persons were evaluated. The rate of serum ALT improved in subjects with more than 5% weight loss, and also the rate of serum ALT in 136 subjects reached to normal rate. In a clinical trial, 152 participants with increased liver enzymes were divided into two groups randomly. One group had more lifestyle modification but the other group had

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

less (nutrition and physical activity). At the end of the study, the rate of reduction in the hepatic enzymes was higher in the group with more modification in the lifestyle than other group.[89] 67 individuals with fatty liver participated in a study. Once a month, they were visited by practitioner and also once every three months they were consulted by nutritionist. In addition, they had equal lifestyle modification (increased physical activity and they received a weight loss diet). At the end of six months, the interference of hepatic enzymes and the ratio of liver to spleen improved in these people.[90] Determining the therapeutic effect of weight loss in the clinical trial has two restrictions as follow: the first restriction is due to the little number of samples in the study and the second one is to determine the effect of weight loss on liver histology because liver biopsy is performed in the studies due to ethical considerations. The liver biopsy is essential for evaluating the effect of weight loss on hepatic steatosis. This is important because some diets apparently decrease the hepatic enzymes, but they cause damage of liver. The noninvasive methods should be used for evaluating the histological features of liver and they determine the real effect of weight loss on liver. Nevertheless, in the reviewed studies the weight loss improved the liver function. Weight loss has been confirmed as therapeutic method.

PHYSICAL ACTIVITY

Higher physical activity is beneficial for people. It decreases the risk of developing diabetes type II, insulin resistance, blood pressure, dyslipidemia, impaired glucose tolerance and metabolic syndrome.[91-95] The studies demonstrated that physical activity play key role in treatment of patients with non-alcoholic fatty liver. Several observational studies showed that there is reverse correlation between prevalence of fatty liver to the time of physical activity. In one study with more samples, 349 individuals with fatty liver spent less time for physical activity (aerobic and resistance exercises).[96] In the other study with 218 participants, there was reverse correlation between physical fitness and developing fatty liver.[97] In one study on 37 persons with non-alcoholic fatty liver, hepatic biopsy demonstrated that patients with lower physical activity had higher steatosis in liver.[98] The useful effects of physical activity have been supported by recent clinical trials. In a clinical trial on 141 participants with non-alcoholic fatty liver, the subjects were given instruction for physical activity during 3 months. After three months, the weight of persons with physical activity >60 minutes/week significantly decreased (mean 2.4 kg), and also their insulin resistance and hepatic enzymes reduced.[99] In other clinical trial, the aerobic physical activity along with a low energy diet helped to normalizing the level of hepatic enzymes.[100] Therefore, it appeared that increased physical activity improves the level of hepatic enzymes. In a clinical trial on 19 subjects with obesity, the short time effect of aerobic physical activity on liver, blood, visceral fats and muscular lipid was evaluated by using magnetic resonance imaging (MRI). Cycling for four weeks (three sessions per week for 30 to 45 minutes) meaningfully decreased the rate of plasma TG up to 4%, the rate of visceral fats up to 12%, and the rate of hepatic TG up to 21%. It should be considered that these changes were produced without weight loss.[101] For three months, a study has been done on 12 obese subjects with fatty liver. They received the resistance exercise program including two one-hour sessions per week. The physical activity increased the strength and muscularity in participants. Although, the rate of fatty liver did not change, but the rate of insulin resistance was increased without weight loss.[102,103] Physical activity causes weight loss and it likely results in increased insulin resistance and glucose homeostasis.[104] Physical activity increases insulin receptors in muscles. As a result, the rate of glucose inflow into the muscles is elevated.[105] Also, physical activity has beneficial effect on fatty acids oxidation by increasing the rate of oxidation.[106] TG concentration will be decreased by higher physical activity.[107] The rate of removal of free fatty acids in plasma is decreased in athletes than non-athletes people.[108] The similar findings in monozygote twins defined that increased physical activity in one of them (due to the lack of genetic impairment effect) decreases the fatty acids removal by liver.[106] In the recent years, there is great attention to resistance exercises for increasing the physical activity.[109-111] A study demonstrated that resistance exercises significantly reduce the rate of visceral fat and also it increases the lipid indices.[112] A randomized clinical trial showed the effect of aerobic and resistance exercises on cardiovascular diseases. Resistance exercises not only increase the rate of lean body mass but also decrease the rate of total fat of body.[113] In one meta-analysis study, the aerobic and resistance exercises were compared and the resistance exercise increased the lean body mass than aerobic one.[114] Increased the volume of muscle through increasing the area of reserving glucose reduces the required insulin for normalizing the level of glucose.[115] The US Centers of Prevention and Control of Diseases (CDC) recommend that healthy people do more than 30 minutes moderate to severe activity, all days per week, and also they should do resistance exercises more than 3 times a week for >20 minutes in each session. However, these instructions extensively have been recommended, only 27.7% American adults do the moderate to vigorous physical activity and 29.2% do not have any regular activity.[116,117] In addition, the prevalence of physical activity in adults with diabetes is very less than non-diabetic people.[118] People with diabetes less likely perform the recommendations related to physical activity.[119,120] In one study, the time of sedentary life of persons was measured. The sedentary time had direct correlation to the rate of fasting insulin.[121] Environmental factors such as driving by car instead of walking, sedentary activity and watching TV reduce physical activity.[122]

DIETARY SUPPLEMENTS

Vitamin E

Vitamin therapy with high dose vitamin E supplement as 1000-300 IU/day (recommended as approximately 30 IU/daily) has been associated with conflict results. In the uncontrolled clinical trials, receiving the vitamin E was associated with reduced hepatic enzymes[123]; however, simultaneously using of vitamin E, lifestyle modification, diet and physical activity in controlled

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

trials did not show the therapeutic effects of vitamin E.[124,125] In randomized clinical trial, 247 patients with non-alcoholic fatty liver randomly divided to three groups: the first group was given 30 mg/day pigolitazone, the second group was given 800 IU/day vitamin E, and the third group received placebo. The duration of this study was 2 years. There was significantly improvement in non-alcoholic fatty liver by vitamin E therapy compare to placebo. Vitamin E and pigolitazone reduced ALT, AST and the rate of steatosis than placebo, but the rate of hepatic fibrosis did not change.[126] Nevertheless, some clinical trials demonstrated that using high dose vitamin E causes stroke and death due to different reasons.[127,128]

Vitamin D

Many studies have suggested than vitamin D potentially play key role in decreasing the development of diabetes type 2, hypertension, and cardiovascular diseases.[129-131] The level of vitamin D of serum independently is related to the beta cells functions and insulin sensitivity in patients with diabetes type II.[132] In one study, the level of serum vitamin D was low in patients with non-alcoholic fatty liver.[133] In a study, Targer et al[133] compared 60 patients with non-alcoholic fatty liver 60 healthy individuals in terms of the level of serum vitamin D. the level of serum vitamin D in the group with non-alcoholic fatty liver was very lower than healthy individuals. In patients with non-alcoholic fatty liver, the level of serum vitamin D was related to the level of steatosis, inflammation and hepatic fibrosis. In one study, the relationship between vitamin D of serum, fatty liver and cardiac diseases was evaluated. In this study, 670 patients with non-alcoholic fatty liver were compared to 30 healthy individuals. Patients with non-alcoholic fatty liver had very lower level of serum vitamin D than control group.[134] Eventually, further investigations are required for evaluating the correlation between the level of serum vitamin D, non-alcoholic fatty liver and the therapeutic effects of serum vitamin D on non-alcoholic fatty liver.

CONCLUSION

Non-alcoholic fatty liver not only is a chronic hepatic disease but also it predisposed to development of diabetes type II.[133-137] Also, in some studies the non-alcoholic fatty liver is related to cardiovascular diseases.[138-144] It is important to know the risk factors which result in non-alcoholic fatty liver because prevention of these risk factors can reduce the risk of non-alcoholic fatty liver. The relationship between nutrition to non-alcoholic fatty liver in human and animal has been confirmed.[22,36,47,65,73,85,143] Nevertheless, most observational and retrospective studies have been done in this field. Therefore, the nutritional studies relate to dietary recall have some restrictions such as more or less estimation for taking the food. For removing these restrictions, various recalls should be obtained from patient with non-alcoholic fatty liver.[145] Also, the large prospective studies and more clinical trials shall be performed for determining the correlation between non-alcoholic fatty liver and nutrition. Today, there is not any stable recommendation as therapeutic strategy for patients with non-alcoholic fatty liver (due to the lack of qualified studies about non-alcoholic fatty liver). With regard to the available data, the weight loss more than 5-10% results in the decreased level of steatosis.[146] In addition, the healthy nutrition is very important in these diseases. Therefore, these patients should be instructed about the way of healthy nutrition. The patients should be recommended that not only decrease the rate of consumption the trans and saturated fatty acids but also they should increase intake of the polyunsaturated fatty acids, specially omega 3. Patients with non-alcoholic fatty liver should decrease drinking the sweetened beverages and also they should increase consuming the vegetables and fruits rich of fiber.[147] They should reduce to consume the red meat and fast foods; however, eating the fish should be increased. Physical activity should be considered as a part of treatment. Increasing the duration of physical activity causes significantly improvement in non-alcoholic fatty liver.[148] The treatment team for patients with this disease should be consisted of dietician, psychology, and expert of physical exercise[149-151] so as to achieve the therapeutic purposes.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Sanyal AJ. Technical review on non-alcoholic fatty liver disease. *Gastroenterology.* 2002; 123: 1705-1725. doi: 10.1053/gast.2002.36572

2. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population based study and its association with biochemical and anthropometric measures. *Liver Int.* 2006; 26: 856-863. doi: 10.1111/j.1478-3231.2006.01311.x

3. Neuschwander-Tetri BA, Caldwell SH. Non-alcoholic steatohepatitis: Summary of an AASLD single topic conference. *Hepatology.* 2003; 37: 1202-1219. doi: 10.1053/jhep.2003.50193

4. Angulo P. Non-alcoholic fatty liver disease. *N Engl J Med.* 2002; 346: 1221-1231. doi: 10.1056/NEJMra011775

5. Propst A, Propst T, Judmaier G, Vogel W. Prognosis in non-alcoholic steatohepatitis. *Gastroenterology.* 1995; 108: 1607.

6. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of non-alcoholic steatosis syndromes. *Semin Liver Dis.* 2001; 21: 17-26. Web site. http://www.ncbi.nlm.nih.gov/pubmed/11296693. Accessed June 27, 2016

7. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med.* 2000; 132: 112-117. doi: 10.7326/0003-4819-132-2-200001180-00004

8. Bedogni G, Bellentani S. Fatty liver: How frequent is it and

why? *Ann Hepatol.* 2004; 3: 63-65. Web site. http://www.medigraphic.com/pdfs/hepato/ah-2004/ah042d.pdf. Accessed June 27, 2016

9. Marchesini G, Bugianesi E, Forlani G, et al. Non-alcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology.* 2003; 37: 917-923. doi: 10.1053/jhep.2003.50161

10. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of non-alcoholic fatty liver disease with insulin resistance. *Am J Med.* 1999; 107: 450-455. doi: 10.1016/S0002-9343(99)00271-5

11. Del Gaudio A, Boschi L, Del Gaudio GA, Mastrangelo L, Munari D. Liver damage in obese patients. *Obes Surg.* 2002; 12: 802-804. doi: 10.1381/096089202320995592

12. Gupte P, Amarapurkar D, Agal S, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. *J Gastroenterol Hepatol.* 2004; 19: 854-858. doi: 10.1111/j.1440-1746.2004.03312.x

13. Angelico F**,** Del Ben M, Conti R, et al. Insulin resistance, the metabolic syndrome, andnon-alcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2005; 90: 1578-1582. doi: 10.1210/jc.2004-1024#sthash.TTXOh4G5.dpuf

14. Lonardo A, Lombardini S, Scaglioni F, et al. Hepatic, steatosis and insulin resistance: Does etiology make a difference? *J Hepatol.* 2006; 44: 190-196. doi: 10.1016/j.jhep.2005.06.018

15. Marchesini G, Marzocchi R, Agostini F, Bugianesi E. Non-alcoholic fatty liver disease and the metabolic syndrome. *Curr Opin Lipidol.* 2005; 16: 421-427. Web site. http://journals.lww.com/co-lipidology/Abstract/2005/08000/Non-alcoholic_fatty_liver_disease_and_the_metabolic.6.aspx. Accessed June 27, 2016

16. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as apredictor of non-alcoholic fatty liver disease. *Ann Intern Med.* 2005; 143: 722-728. doi: 10.7326/0003-4819-143-10-200511150-00009

17. Yasutake K, Nakamuta M, Shima Y, et al. Nutritional investigation of non-obese patientswith non-alcoholic fatty liver disease: The significance of dietary cholesterol. *Scand J Gastroenterol*. 2009; 44: 471-477. doi: 10.1080/00365520802588133

18. Musso G, Gambino R, De Michieli F, et al. Dietary habits andtheir relations to insulin resistance and postprandial lipemiain non-alcoholic steatohepatitis. *Hepatology.* 2003; 37: 909-916. doi: 10.1053/jhep.2003.50132

19. Assy N, Nasser G, Kamayse I, et al. Soft drink consumption linked withfatty liver in the absence of traditional risk factors. *Can J Gastroenterol.* 2008; 22: 811-816. doi: 10.1155/2008/810961

20. Banerji MA, Faridi N, Atluri R, Chaiken RL, Lebovitz HE. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. *J Clin Endocrinol Metab*. 1998; 84: 137-144. doi: 10.1210/jcem.84.1.5371#sthash.1ZiBQiq2.dpuf

21. Lee JH, Rhee PL, Lee JK, et al. Role of hyperinsulinemia and glucose intolerance in the pathogenesis of non-alcoholic fatty liver in patients with normal body weight. *Korean J Intern Med*. 1998; 13: 10-14. doi: 10.3904/kjim.1998.13.1.10

22. Marchesini G, Brizi M, Bianchi G, et al. Non-alcoholic fatty liver disease: A feature of the metabolic syndrome. *Diabetes.* 2001; 50: 1844-1850. doi: 10.2337/diabetes.50.8.1844

23. Pagano G, Pacini G, Musso G, et al. Non-alcoholic steatohepatitis, insulin resistance, and metabolicsyndrome: Further evidence for an etiologic association. *Hepatology.* 2002; 35: 367-372. doi: 10.1053/jhep.2002.30690

24. Chitturi S, Abeygunasekera S, Farrell GC, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology.* 2002; 35: 373-379. doi: 10.1053/jhep.2002.30692

25. Cheung O, Sanyal AJ. Recent advances in non-alcoholic fatty liver disease. *Curr Opin Gastroenterol.* 2010; 26: 202-208.

26. Koteish A, Diehl AM. Animal models of steatosis. *Semin Liver Dis.* 2001; 21: 89-104. Web site. http://www.ncbi.nlm.nih.gov/pubmed/11296700. Accessed June 27, 2016

27. Andersen T, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol.* 1991; 12: 224-229. doi: 10.1016/0168-8278(91)90942-5

28. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Non-alcoholic fatty liver disease: Improvement in liver histological analysis with weight loss. *Hepatology.* 2004; 39: 1647-1654. doi: 10.1002/hep.20251

29. Eriksson S, Eriksson KF, Bondesson L. Non-alcoholic steatohepatitis in obesity: A reversible condition. *Acta Med Scand.* 1986; 220: 83-88. doi: 10.1111/j.0954-6820.1986.tb02733.x

30. Luyckx FH, Desaive C, Thiry A, et al. Liver abnormalities in severely obese subjects: Effect of drastic weight loss after gastroplasty. *Int J Obes Relat Metab Disord.* 1998; 22: 222-226. Web site. http://www.ncbi.nlm.nih.gov/pubmed/9539189. Accessed June 27, 2016

31. Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology.* 1990; 99: 1408-1413. Web site. http://www.ncbi.nlm.nih.gov/pubmed/2210247. Accessed June 27, 2016

32. Ueno T, Sugawara H, Sujaku K, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol.* 1997; 27: 103-107. doi: 10.1016/S0168-

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

8278(97)80287-5

33. 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.* 2009; 17: 2162-2168. doi: 10.1038/oby.2009.126

34. Katan MB. Weight-loss diets for the prevention and treatment of obesity. *N Engl J Med.* 2009; 360: 923-925. doi: 10.1056/NEJMe0810291

35. Heath RB, Karpe F, Milne RW, Burdge GC, Wootton SA, Frayn KN. Selective partitioning of dietary fatty acids into the VLDL TG pool in the early postprandial period. *J Lipid Res.* 2003; 44: 2065-2072. doi: 10.1194/jlr.M300167-JLR200

36. Westerbacka J, Lammi K, Hakkinen AM, et al. Dietary fat content modifies liver fat in overweight nondiabetic subjects. *J Clin Endocrinol Metab.* 2005; 90: 2804-2809. doi: 10.1210/jc.2004-1983#sthash.f50f9cxy.dpuf

37. Musso G, Gambino R, De Michieli F, et al. Dietary habits and their relations to insulin resistance and postprandial lipemiain non-alcoholic steatohepatitis. *Hepatology.* 2003; 37: 909-916. doi: 10.1053/jhep.2003.50132

38. McCuskey RS, Ito Y, Robertson GR, McCuskey MK, Perry M, Farrell GC. Hepatic microvascular dysfunction during evolution of dietary steatohepatitis in mice. *Hepatology.* 2004; 40: 386-393. doi: 10.1002/hep.20302

39. Samuel VT, Liu ZX, Qu X, et al. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *J Biol Chem.* 2004; 279: 32345-32353. doi: 10.1074/jbc.M313478200

40. Kim SP, Ellmerer M, Van Citters GW, Bergman RN. Primacy of hepatic insulin resistance in the development of the metabolic syndrome induced by an isocaloric moderate-fat diet in the dog. *Diabetes*. 2003; 52: 2453-2460. doi: 10.2337/diabetes.52.10.2453

41. Solga S, Alkhuraishe AR, Clark JM, et al. Dietary composition and non-alcoholic fatty liver disease. *Dig Dis Sci.* 2004; 49: 1578-1583. doi: 10.1023/B:DDAS.0000043367.69470.b7

42. Toshimitsu K, Matsuura B, Ohkubo I, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. *Nutrition.* 2007; 23: 46-52. doi: 10.1016/j.nut.2006.09.004

43. Machado MV, Ravasco P, Jesus L, et al. Blood oxidative stress markers in non-alcoholic steatohepatitis and how it correlates with diet. *Scand J Gastroenterol*. 2008; 43: 95-102. doi: 10.1080/00365520701559003

44. Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS. Fish oil prevents insulin resistance induced by high-fat feeding in rats. *Science.* 1987; 237: 885-888. doi: 10.1126/science.3303333

45. Sekiya M, Yahagi N, Matsuzaka T, et al. Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression. *Hepatology.* 2003; 38: 1529-1539. doi: 10.1016/j.hep.2003.09.028

46. Levy JR, Clore JN, Stevens W. Dietary n-3 polyunsaturated fatty acids decrease hepatic triglycerides in Fischer 344 rats. *Hepatology.* 2004; 39: 608-616. doi: 10.1002/hep.20093

47. 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. doi: 10.1016/j.clnu.2006.01.027

48. Capanni M, Calella F, Biagini MR, et al. 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. doi: 10.1111/j.1365-2036.2006.02885.x

49. Tanaka N, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves non-alcoholic steatohepatitis. *J Clin Gastroenterol.* 2008; 42: 413-418. doi: 10.1097/MCG.0b013e31815591aa

50. Ibrahim A, Natrajan S, Ghafoorunissa R. Dietary trans-fatty acids alter adipocyte plasma membrane fatty acid composition and insulin sensitivity in rats. *Metabolism.* 2005; 54: 240-246. Web site. http://www.ncbi.nlm.nih.gov/pubmed/15789505. Accessed June 27, 2016

51. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med.* 1997; 337: 1491-1499. doi: 10.1056/NEJM199711203372102

52. Machado RM, Stefano JT, Oliveira CP, et al. Intake of trans fatty acids causes non-alcoholic steatohepatitis and reduces adipose tissue fat content. *J Nutr.* 2010; 140: 1127-1132. doi: 10.3945/jn.109.117937

53. Tetri LH, Basaranoglu M, Brunt EM, Yerian LM, Neuschwander-Tetri BA. Severe NAFLD with hepatic necroinflammatory changes in mice fed trans fats and a high-fructose corn syrup equivalent. *Am J Physiol Gastrointest Liver Physiol.* 2008; 295: G987-G995. doi: 10.1152/ajpgi.90272.2008

54. 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. *Am J Clin Nutr.* 2003; 77: 1146-1155. Web site. http://ajcn.nutrition.org/content/77/5/1146.full. Accessed June 27, 2016

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

55. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: A meta-analysis. *Am J Clin Nutr.* 1998; 67: 577S-582. Web site. http://www.ncbi.nlm.nih.gov/pubmed/9497173. Accessed June 27, 2016

56. Hussein O, Grosovski M, Lasri E, Svalb S, Ravid U, Assy N. Monounsaturated fat decreases hepatic lipid content innonalcoholic fatty liver disease in rats. *World J Gastroenterol.* 2007; 13: 361-368. doi: 10.3748/WJG.v13.i3.361

57. Hernandez R, Martinez-Lara E, Canuelo A, et al. Steatosis-recovery after treatment with a balanced sunflower orolive oil-based diet: Involvement of perisinusoidal stellatecells. *World J Gastroenterol.* 2005; 11: 7480-7485. doi: 10.3748/wjg.v11.i47.7480

58. Szende B, Timar F, Hargitai B. Olive oil decreases liver damage in rats caused by carbon tetrachloride (CCl4). *Exp Toxicol Pathol.* 1994; 46: 355-359. doi: 10.1016/S0940-2993(11)80116-8

59. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): A population based study. *J Hepatol.* 2007; 47: 711-717. doi: 10.1016/j.jhep.2007.06.020

60. Kainuma M, Fujimoto M, Sekiya N, et al. Cholesterol-fed rabbit as a unique model of non-alcoholic, nonobese, non-insulin-resistant fatty liver disease with characteristic fibrosis. *J Gastroenterol.* 2006; 41: 971-980. doi: 10.1007/s00535-006-1883-1

61. Gaby AR. Adverse effects of dietary fructose. *Altern Med Rev*. 2005; 10: 294-306. Web site. http://www.altmedrev.com/publications/10/4/294.pdf. Accessed June 27, 2016

62. Brownell KD, Farley T, Willett WC, et al. The public health and economic benefits of taxing sugar-sweetened beverages. *N Engl J Med.* 2009; 361: 1599-1605. doi: 10.1056/NEJMhpr0905723

63. Duffey KJ, Popkin BM. Shifts in patterns and consumption of beverages between 1965 and 2002. *Obesity.* 2007; 15: 2739-2747. doi: 10.1038/oby.2007.326

64. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004; 292: 927-934. doi: 10.1001/jama.292.8.927

65. Poulsom R. Morphological changes of organs after sucrose or fructose feeding. *Prog Biochem Pharmacol.* 1986; 21: 104-134. Web site. http://www.ncbi.nlm.nih.gov/pubmed/3523499. Accessed June 27, 2016

66. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. *Am J Clin Nutr.* 2006; 84: 274-288. Web site. http://www.ncbi.nlm.nih.gov/pubmed/16895873. Accessed June 27, 2016

67. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007; 97: 667-675. doi: 10.2105/AJPH.2005.083782

68. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr.* 2009; 89: 1037-1042. doi: 10.3945/ajcn.2008.27140

69. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. *Diabetes Care.* 2010; 33: 2477-2483. doi: 10.2337/dc10-1079

70. Herman RH, Zakim D, Stifel FB. Effect of diet on lipid metabolism in experimental animals and man. *Fed Proc.* 1970; 29: 1302-1307. Web site. http://www.ncbi.nlm.nih.gov/pubmed/4245709. Accessed June 27, 2016

71. Cave M, Deaciuc I, Mendez C, et al. Non-alcoholic fatty liver disease: predisposing factors and the role of nutrition. *J Nutr Biochem.* 2007; 18: 184-195. doi: 10.1016/j.jnutbio.2006.12.006

72. Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol.* 2008; 48: 993-999. doi: 10.1016/j.jhep.2008.02.011

73. 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. doi: 10.1016/j.jhep.2009.05.033

74. Abdelmalek MF, Suzuki A, Guy C, et al. Increased fructose consumption is associated with fibrosis severity in patients with non-alcoholic fatty liver disease. *Hepatology.* 2010; 51: 1961-1971. doi: 10.1002/hep.23535

75. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am J Clin Nutr.* 2000; 72: 912-921. Web site. http://www.ncbi.nlm.nih.gov/pubmed/11010931. Accessed June 27, 2016

76. Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet.* 2005; 365: 36-42. doi: 10.1016/S0140-6736(04)17663-0

77. Kechagias S, Ernersson A, Dahlqvist O, et al. Fast-food-based hyper-alimentation can induce rapid and profound elevation of serum alanine aminotransferase in healthy subjects. *Gut.* 2008; 57: 649-654. doi: 10.1136/gut.2007.131797

78. Marchesini G, Ridolfi V, Nepoti V. Hepatotoxicity of fast food? *Gut.* 2008; 57: 568-570. doi: 10.1136/gut.2007.143958

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

79. Rozental P, Biava C, Spencer H, Zimmerman HJ. Liver morphology and function tests in obesity and during total starvation. *Am J Dig Dis.* 1967; 12: 198-208. doi: 10.1007/BF02233443

80. 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. doi: 10.1056/NEJM197004092821502

81. Andersen T, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol*. 1991; 12: 224-229. Web site. http://www.ncbi.nlm.nih.gov/pubmed/2051001. Accessed June 27, 2016

82. Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. *Gastroenterology.* 1990; 99: 1408-1413. Web site. http://www.ncbi.nlm.nih.gov/pubmed/2210247. Accessed June 27, 2016

83. Ueno T, Sugawara H, Sujaku K, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol.* 1997; 27: 103-107. doi: 10.1016/S0168-8278(97)80287-5

84. Huang MA, Greenson JK, Chao C, et al. 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. doi: 10.1111/j.1572-0241.2005.41334.x

85. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on non-alcoholic steatohepatitis. *Hepatology.* 2010; 51: 121-129. doi: 10.1002/hep.23276

86. Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with non-alcoholic steatohepatitis: A randomized, prospective trial. *Hepatology.* 2009; 49: 80-86. doi: 10.1002/hep.22575

87. Lazo M, Solga SF, Horska A, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care.* 2010; 33: 2156-2163. doi: 10.2337/dc10-0856

88. Suzuki A, Lindor K, St Saver J, et al. Effect of changes on body weight and lifestyle in non-alcoholic fatty liver disease. *J Hepatol.* 2005; 43: 1060-1066. doi: 10.1016/j.jhep.2005.06.008

89. St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Effect of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. *J Gastroenterol Hepatol.* 2009; 24: 399-407. doi: 10.1111/j.1440-1746.2008.05694.x

90. Oza N, Eguchi Y, Mizuta T, et al. A pilot trial of body weight reduction for non-alcoholic fatty liver disease with a home-based lifestyle modification intervention delivered in collaboration with interdisciplinary medical staff. *J Gastroenterol*. 2009; 44: 1203-1208. doi: 10.1007/s00535-009-0115-x

91. Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW 3rd, Blair SN. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: A randomized trial. *JAMA*. 1999; 281: 327-334. doi: 10-1001/pubs.JAMA-ISSN-0098-7484-281-4-joc80889

92. 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.* 2005; 99: 1193-1204. doi: 10.1152/japplphysiol.00160.2005

93. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol.* 2005; 99: 1205-1213. doi: 10.1152/japplphysiol.00193.2005

94. Bauman AE. Updating the evidence that physical activity is good for health: An epidemiological review 2000-2003. *J Sci Med Sport.* 2004; 7: 6-19. Web site. http://www.ncbi.nlm.nih.gov/pubmed/15214597. Accessed June 27, 2016

95. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care.* 1997; 20: 537-544. doi: 10.2337/diacare.20.4.537

96. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Role of leisure-time physical activity in non-alcoholic fatty liver disease: A population-based study. *Hepatology.* 2008; 48: 1791-1798. doi: 10.1002/hep.22525

97. Church TS, Kuk JL, Ross R, Priest EL, Biltoft E, Blair SN. Association of cardiorespiratory fitness, body mass index, and waist circumference to non-alcoholic fatty liver disease. *Gastroenterology.* 2006; 130: 2023-2030. doi: 10.1053/j.gastro.2006.03.019

98. Krasnoff JB, Painter PL, Wallace JP, Bass NM, Merriman RB. Health-related fitness and physical activity in patients with non-alcoholic fatty liver disease. *Hepatology.* 2008; 47: 1158-1166. doi: 10.1002/hep.22137

99. St. George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with non-alcoholic fatty liver disease. *Hepatology.* 2009; 50: 68-76. doi: 10.1002/hep.22940

100. Sreenivasa Baba C, Alexander G, Kalyani B, et al. Effect of exercise and dietary modification on serum aminotransferase levels in patients with non-alcoholic steatohepatitis. *J Gastroenterol Hepatol.* 2006; 21: 191-198. doi: 10.1111/j.1440-1746.2005.04233.x

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

101. 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: 1105-1112. doi: 10.1002/hep.23129

102. Kantartzis K, Thamer C, Peter A, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. *Gut.* 2009; 58: 1281-1288. doi: 10.1136/gut.2008.151977

103. Van Der Heijden GJ, Wang ZJ, Chu Z, et al. Strength exercise improves muscle mass and hepatic insulin sensitivity in obese youth. *Med Sci Sports Exerc*. 2010; 42: 1973-1980. doi: 10.1249/MSS.0b013e3181df16d9

104. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials. *JAMA.* 2001; 286: 1218-1227. doi: 10.1001/jama.286.10.1218

105. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med.* 1998; 49: 235-261. doi: 10.1146/annurev.med.49.1.235

106. Hannukainen JC, Nuutila P, Borra R, et al. Increased physical activity decreases hepatic free fatty acid uptake: A study in human monozygotic twins. *J Physiol.* 2007; 578: 347-358. doi: 10.1113/jphysiol.2006.121368

107. Tamura Y, Tanaka Y, Sato F, et al. Effects of diet and exercise on muscle and liver intracellular lipid contents and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2005; 90: 3191-3196. doi: 10.1210/jc.2004-1959#sthash.hkbBx0DQ.dpuf

108. Iozzo P, Takala T, Oikonen V, et al. Effect of training status on regional disposal of circulating free fatty acids in the liver and skeletal muscle during physiological hyperinsulinemia. *Diabetes Care*. 2004; 27: 2172-2177. doi: 10.2337/diacare.27.9.2172

109. Albright A, Franz M, Hornsby G, et al. American College of Sports Medicine position stand: Exercise and type 2 diabetes. *Med Sci Sports Exerc*. 2000; 32: 1345-1360. Web site. http://www.ncbi.nlm.nih.gov/pubmed/10912903. Accessed June 27, 2016

110. Pollock ML, Franklin BA, Balady GJ, et al. 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. doi: 10.1161/01.CIR.101.7.828

111. Ibanez J, Izquierdo M, Arguelles I, et al. 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. doi: 10.2337/diacare.28.3.662

112. Tsuzuku S, Kajioka T, Endo H, Abbott RD, Curb JD, Yano K. Favorable effects of non-instrumental resistance training on fat distribution and metabolic profiles in healthy elderly people. *Eur J Appl Physiol.* 2007; 99: 549-555. doi: 10.1007/s00421-006-0377-4

113. Banz WJ, Maher MA, Thompson WG, et al. Effects of resistance versus aerobic training on coronary artery disease risk factors. *Exp Biol Med.* 2003; 228: 434-440. Web site. http://ebm.sagepub.com/content/228/4/434.long. Accessed June 27, 2016

114. Ballor DL, Keesey RE. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int J Obes.* 1991; 15: 717-726. Web site. http://www.ncbi.nlm.nih.gov/pubmed/1838100. Accessed June 27, 2016

115. Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. *Med Sci Sports Exerc.* 1984; 16: 539-543. Web site. http://www.ncbi.nlm.nih.gov/pubmed/6392812. Accessed June 27, 2016

116. Pratt M, Macera CA, Blanton C. Levels of physical activity and inactivity in children and adults in the United States: Current evidence and research issues. *Med Sci Sports Exerc.* 1999; 31: S526-S533. Web site. http://www.ncbi.nlm.nih.gov/pubmed/10593523. Accessed June 27, 2016

117. Peterson JA. Get moving! Physical activity counseling in primary care. *J Am Acad Nurse Pract*. 2007; 19: 349-357. doi: 10.1111/j.1745-7599.2007.00239.x

118. Morrato EH, Hill JO, Wyatt HR, Ghushchyan V, Sullivan PW. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care.* 2007; 30: 203-209. doi: 10.2337/dc06-1128

119. Zhao G, Ford ES, Li C, Mokdad AH. Compliance with physical activity recommendations in US adults with diabetes. *Diabet Med*. 2008; 25: 221-227. doi: 10.1111/j.1464-5491.2007.02332.x

120. Newton JL, Jones DE, Henderson E, et al. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut.* 2008; 57: 807-813. doi: 10.1136/gut.2007.139303

121. 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: 1776-1779. doi: 10.2337/db08-1773

122. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, et al. Diet and lifestyle recommendations

revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation.* 2006; 114: 82-96. doi: 10.1161/CIRCULATIONAHA.106.176158

123. Hasegawa T, Yoneda M, Nakamura K, Makino I, Terano A. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with non-alcoholic steatohepatitis: A pilot study. *Aliment Pharmacol Ther.* 2001; 15: 1667-1672. doi: 10.1046/j.1365-2036.2001.01083.x

124. Kugelmas M, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: A pilot study of the effects of lifestyle modification and vitamin E. *Hepatology.* 2003; 38: 413-419. doi: 10.1053/jhep.2003.50316

125. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with non-alcoholic steatohepatitis. *Am J Gastroenterol.* 2003; 98: 2485-2490. doi: 10.1111/j.1572-0241.2003.08699.x

126. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for non-alcoholic steatohepatitis. *N Engl J Med.* 2010; 362: 1675-1685. doi: 10.1056/NEJMoa0907929

127. Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: The physicians' health study II randomized controlled trial. *JAMA*. 2008; 300: 2123-2133. doi: 10.1001/jama.2008.600

128. 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 Syst Rev.* 2008; CD007176. doi: 10.1002/14651858.CD007176.pub2

129. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes: A systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2007; 92: 2017-2029. doi: 10.1210/jc.2007-0298#sthash.zVEDzof1.dpuf

130. 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. doi: 10.1016/j.atherosclerosis.2008.10.033

131. Pittas AG, Chung M, Trikalinos T, et al. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med.* 2010; 152: 307-314. doi: 10.7326/0003-4819-152-5-201003020-00009

132. Kayaniyil S, Vieth R, Retnakaran R, et al. Association of vitamin D with insulin resistance and beta-cell dysfunction in subjects at risk for type 2 diabetes. *Diabetes Care.* 2010; 33: 1379-1381. doi: 10.2337/dc09-2321

133. Targher G, Bertolini L, Scala L, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis.* 2007; 17: 517-524. doi: 10.1016/j.numecd.2006.04.002

134. Nseir WMA, Abu Mouch S, Grosovski M, Assy N. Association between 25-OH vitamin D concentrations and risk of coronary artery disease in patients with non alcoholic fatty liver disease. *Hepatology.* 2010; 52(Suppl 1).

135. Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes.* 2002; 51: 1889-1895. doi: 10.2337/diabetes.51.6.1889

136. Hanley AJ, Williams K, Festa A, et al. Insulin resistance atherosclerosis study. Elevations in markers of liver injury and risk of type 2 diabetes: The insulin resistance atherosclerosis study. *Diabetes.* 2004; 53: 2623-2632. doi: 10.2337/diabetes.53.10.2623

137. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. *Diabetes Care.* 2005; 28: 2913-2918. doi: 10.2337/diacare.28.12.2913

138. Marchesini G, Forlani G. NASH: From liver diseases to metabolic disorders and back to clinical hepatology. *Hepatology.* 2002; 35: 497-499. doi: 10.1053/jhep.2002.31551

139. Fracanzani AL, Burdick L, Rasselli S, et al. Risk of early atherosclerosis evaluated by carotid artery intima-media thickness in patients with NAFLD: A case control study. *J Hepatol.* 2006; 44: S39.

140. Ekstedt M, Fran'zen LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Survival and causes of death in patients with elevated liver enzymes associated with NAFLD. *J Hepatol*. 2006; 44: S40.

141. Villanova N, Moscatiello S, Ramilli S, et al. Endothelial dysfunction and cardiovascular risk profile in non-alcoholic fatty liver disease. *Hepatology.* 2005; 42: 473-480. doi: 10.1002/hep.20781

142. Targher G, Bertolini L, Poli F, et al. Non-alcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes.* 2005; 54: 3541-3546. doi: 10.2337/diabetes.54.12.3541

143. Jepsen P, Vilstrup H, Mellemkjaer L, et al. Prognosis of patients with a diagnosis of fatty liver-a registry-based cohort study. *Hepatogastroenterology.* 2003; 50: 2101-2104. Web site. http://www.ncbi.nlm.nih.gov/pubmed/14696473. Accessed June 27, 2016

144. Kessler A, Levy Y, Roth A, et al. Increased prevalence of

ISSN 2377-8350 Open Journal http://dx.doi.org/10.17140/AFTNSOJ-2-130

NAFLD in patients with acute myocardial infarction independent of BMI. *Hepatology.* 2005; 42(Suppl 1): A623.

145. Bogin E, Avidar Y, Merom M. Biochemical changes in liver and blood during liver fattening in rats. *J Clin Chem Clin Biochem.* 1986; 24: 621-626. Web site. http://edoc.hu-berlin.de/oa/degruyter/cclm.1986.24.9.621.pdf. Accessed June 27, 2016

146. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol.* 2010; 53: 372-384. doi: 10.1016/j.jhep.2010.04.008

147. Fabricatore AN. Behavior therapy and cognitive-behavioral therapy of obesity: Is there a difference? *J Am Diet Assoc.* 2007; 107: 92-99. doi: 10.1016/j.jada.2006.10.005

148. Anderson AS. How to implement dietary changes to prevent the development of metabolic syndrome. *Br J Nutr.* 2000; 83(Suppl 1): S165-S168. doi: 10.1017/S0007114500001112

149. Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C. Benefits of lifestyle modification in the pharmacologic treatment of obesity: A randomized trial. *Arch Intern Med*. 2001; 161: 218-227. doi: 10.1001/archinte.161.2.218

150. Marchesini G, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. *J Clin Endocrinol Metab.* 2008; 93: S74-S80. doi: 10.1210/jc.2008-1399

151. Bellentani S, Dalle Grave R, Suppini A, Marchesini G. Fatty Liver Italian Network. Behavior therapy for non-alcoholic fatty liver disease: The need for a multidisciplinary approach. *Hepatology.* 2008; 47: 746-754.