

## Literature Review

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Volume 2 : Issue 2

Article Ref. #: 1000AFTNSOJ2130

### Article History

Received: June 28<sup>th</sup>, 2016

Accepted: August 2<sup>nd</sup>, 2016

Published: August 3<sup>rd</sup>, 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](https://doi.org/10.17140/AFTNSOJ-2-130)

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

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**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.<sup>1-3</sup> In developed country, it is estimated that 20% to 30% of adult populations have non-alcoholic fatty liver.<sup>4-8</sup> 50% of diabetic people and approximately 80% of obese people with morbidity obesity are having non-alcoholic fatty liver.<sup>6,9-10</sup> Prevalence of non-alcoholic fatty liver in Western countries is likely concurrent with epidemic obesity and also it is associated with metabolic disorders.<sup>5,11-14</sup> Patients with non-alcoholic fatty liver usually have insulin resistance.<sup>14-19</sup> 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.<sup>17,18,20,21</sup> In epidemiologic studies, these patients with normal weight have unhealthy diet.<sup>22-24</sup>

The efficacy and immunity of medication therapy is unclear towards treatment of non-alcoholic fatty liver.<sup>25</sup> Obesity has the most correlation with non-alcoholic fatty liver.<sup>26</sup> 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.<sup>27-33</sup>

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.<sup>34</sup> 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.

## 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.<sup>35,36</sup> 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.<sup>37</sup> 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 low 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.<sup>36</sup> 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.<sup>38-40</sup> 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.<sup>41</sup> 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.<sup>5</sup> 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.<sup>37</sup> 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.<sup>42</sup> The relationship between the kind of fat in the diet to the oxidative stress markers was evaluated in patients with non-alcoholic fatty liver.<sup>43,44</sup> 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.<sup>45,46</sup>

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.<sup>44</sup> In addition, it decreases the rate of intra hepatic TG and also it improves steatohepatitis.<sup>45,46</sup>

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.<sup>45</sup> 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.<sup>47</sup> 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-

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.<sup>48</sup> 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.<sup>49</sup> 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.<sup>50,51</sup>

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.<sup>52</sup> 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.<sup>53</sup> 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.<sup>54,55</sup>

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.<sup>56</sup> The rate of hepatosteatosis was improved in the rats that received olive oil associated with balanced diet.<sup>57</sup> Contrary to polyunsaturated oil, olive oil prevents progression of hepatic fibrosis.<sup>58</sup> 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.<sup>47-59</sup> Nevertheless, Musso et al<sup>18</sup> 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.<sup>24</sup> In one study on the non-obese animal models, it was shown that diet rich of cholesterol causes non-alcoholic fatty liver.<sup>60</sup> Increased cholesterol in diet results in increasing the synthesis of fatty acids in hepatic cells.<sup>24</sup> 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.<sup>61</sup> In the recent decades, consumption of sweetened beverages has elevated in the world.<sup>62</sup> The recent studies (2005-2006) demonstrated that children and adults intake 172 and 175 Kcal/day, respectively due to drinking sweetened beverages.<sup>63</sup> 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.<sup>59,64-69</sup>

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.<sup>70</sup> Therefore, it is reasonable that patients with non-alcoholic fatty liver should lower fructose intake.<sup>71</sup> 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.<sup>61</sup> In the recent years, some

studies confirmed the relationship between non-alcoholic fatty liver and consumption of sweetened beverages.<sup>22,59,72,73</sup> 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).<sup>22</sup> 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.<sup>72</sup>

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.<sup>74</sup>

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.<sup>75</sup> The investigators consider Western diet as diet with higher fructose, sweetened beverages,<sup>22,59,72</sup> red meat,<sup>47,59</sup> cholesterol, saturated fatty acids,<sup>47-59</sup> lower fiber,<sup>47</sup> vegetables and fruits.<sup>23</sup> 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.<sup>76</sup> In an animal trial, a diet similar to fast food results in impaired hepatic cells.<sup>53</sup> 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.<sup>77</sup> 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.<sup>78</sup>

## 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,<sup>79,80</sup> 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<sup>81</sup> 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.<sup>82</sup> Two studies with small sample evaluated the effect of a standard diet associated with gradual decreasing of weight on histology of liver.<sup>83</sup> 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.<sup>84</sup>

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).<sup>85</sup> 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, Erlstat was used for decreasing the weight in patients with non-alcoholic fatty liver, and 9% weight loss improved steatosis in these patients.<sup>86</sup> 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.<sup>87</sup>

In a clinical trial by Suzuki et al,<sup>88</sup> 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



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.<sup>89</sup> 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.<sup>90</sup> 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.<sup>91-95</sup> 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).<sup>96</sup> In the other study with 218 participants, there was reverse correlation between physical fitness and developing fatty liver.<sup>97</sup> 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.<sup>98</sup> 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.<sup>99</sup> In other clinical trial, the aerobic physical activity along with a low energy diet helped to normalizing the level of hepatic enzymes.<sup>100</sup> 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.<sup>101</sup> 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.<sup>102,103</sup> Physical activity causes weight loss and it likely results in increased insulin resistance and glucose homeostasis.<sup>104</sup> Physical activity increases insulin receptors in muscles. As a result, the rate of glucose inflow into the muscles is elevated.<sup>105</sup> Also, physical activity has beneficial effect on fatty acids oxidation by increasing the rate of oxidation.<sup>106</sup> TG concentration will be decreased by higher physical activity.<sup>107</sup> The rate of removal of free fatty acids in plasma is decreased in athletes than non-athletes people.<sup>108</sup> 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.<sup>106</sup> In the recent years, there is great attention to resistance exercises for increasing the physical activity.<sup>109-111</sup> A study demonstrated that resistance exercises significantly reduce the rate of visceral fat and also it increases the lipid indices.<sup>112</sup> 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.<sup>113</sup> In one meta-analysis study, the aerobic and resistance exercises were compared and the resistance exercise increased the lean body mass than aerobic one.<sup>114</sup> Increased the volume of muscle through increasing the area of reserving glucose reduces the required insulin for normalizing the level of glucose.<sup>115</sup> 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.<sup>116,117</sup> In addition, the prevalence of physical activity in adults with diabetes is very less than non-diabetic people.<sup>118</sup> People with diabetes less likely perform the recommendations related to physical activity.<sup>119,120</sup> In one study, the time of sedentary life of persons was measured. The sedentary time had direct correlation to the rate of fasting insulin.<sup>121</sup> Environmental factors such as driving by car instead of walking, sedentary activity and watching TV reduce physical activity.<sup>122</sup>

#### 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<sup>123</sup>; however, simultaneously using of vitamin E, lifestyle modification, diet and physical activity in controlled

trials did not show the therapeutic effects of vitamin E.<sup>124,125</sup> In randomized clinical trial, 247 patients with non-alcoholic fatty liver randomly divided to three groups: the first group was given 30 mg/day pioglitazone, 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 pioglitazone reduced ALT, AST and the rate of steatosis than placebo, but the rate of hepatic fibrosis did not change.<sup>126</sup> Nevertheless, some clinical trials demonstrated that using high dose vitamin E causes stroke and death due to different reasons.<sup>127,128</sup>

## Vitamin D

Many studies have suggested that vitamin D potentially play key role in decreasing the development of diabetes type 2, hypertension, and cardiovascular diseases.<sup>129-131</sup> The level of vitamin D of serum independently is related to the beta cells functions and insulin sensitivity in patients with diabetes type II.<sup>132</sup> In one study, the level of serum vitamin D was low in patients with non-alcoholic fatty liver.<sup>133</sup> In a study, Targer et al<sup>133</sup> 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.<sup>134</sup> 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.<sup>133-137</sup> Also, in some studies the non-alcoholic fatty liver is related to cardiovascular diseases.<sup>138-144</sup> 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.<sup>22,36,47,65,73,85,143</sup> 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.<sup>145</sup> 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 stud-

ies 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.<sup>146</sup> 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.<sup>147</sup> 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.<sup>148</sup> The treatment team for patients with this disease should be consisted of dietician, psychology, and expert of physical exercise<sup>149-151</sup> so as to achieve the therapeutic purposes.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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